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A Symposium: Safety of Thrombolytic Agents

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The American Journal of Cardiology®

Introduction

Joel M. Gore, MD, and Richard C. Becker, MD

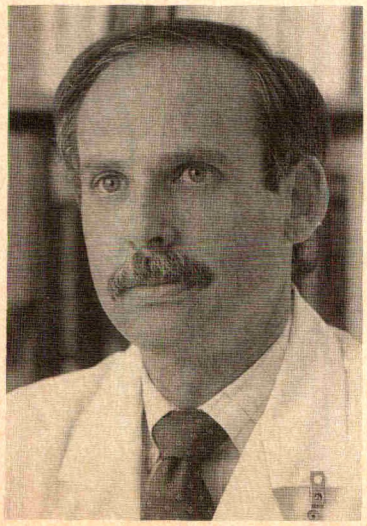
Thrombolytic therapy has become the standard of care for patients with acute myocardial infarction (AMI) in evolution, improving both short- and long-term outcome. However, as with many phases of clinical decision making and acute intervention, the potential risks of treatment must be considered concomitantly with the recognized benefits. Approached in this fashion, the clinician can develop a perspective of net clinical benefit for patient care.

Thrombolytic therapy, with its attendant activation of the fibrinolytic system, carries a risk of bleeding. The pharmacologic action of the agents themselves may unmask underlying vascular pathologic states or protective thrombi, causing clinically evident or occult bleeding. Of the former, intracranial hemorrhagic events are the most feared and potentially devastating. However, neurologic events occur in patients with AMI, including those not receiving thrombolytic therapy. Therefore, the overall impact of thrombolysis remains poorly defined. In the prethrombolytic era, most strokes were attributed to cerebral embolism. With the advent of thrombolytic therapy, however, the occurrence of various forms of intracranial hemorrhage has been reported increasingly. Hemorrhage can occur as a result of primary central nervous system bleeding or at the site of a previous cerebral infarction (hemorrhagic conversion). Significant elevations in systolic or diastolic blood pressure, dose of thrombolytic agent, and prior neurologic disease each appear to be risk factors for severe neurologic events.

Clinically, thrombolytic therapy has been used alone, conjunctively with antiplatelet agents and anticoagulants, combined with coronary angioplasty, or administered in combination with all of these modalities. Therefore, the potential risks and benefits may, in fact, be additive. In choosing a treatment strategy, these factors must be taken into account.

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The major risks of currently available thrombolytic agents include hemorrhage, neurologic events, immunologic complications, systemic hypotension, and myocardial rupture. Thromboembolic events and cardiac rhythm disturbances are rare. In addition, significant hemorrhage is uncommon in patients without underlying vascular disease.

Unfortunately, the routine monitoring of systemic fibrinolytic and anticoagulant parameters has not provided information that can be used to identify individual patients at risk for bleeding. This shortcoming limits the clinician's ability to identify patients at increased risk and, moreover, dictates a defensive posture—treating the events once they occur rather than sighting the potential problem beforehand and acting to prevent it.

The overall clinical benefits of thrombolytic therapy have been limited by two important factors: thrombolytic resistance and reocclusion. There is mounting evidence that increased procoagulant activity at the site of plaque rupture is involved directly in both phenomena. Thrombin and platelet activation appear to play key roles in the procoagulant state; therefore, evolving treatment strategies must focus on methods either to prevent or inhibit focal procoagulant stimuli. Heparin and aspirin have served as the mainstay of conjunctive therapy, but may, in fact, have important limitations. As a result, the development and investigation of newer thrombin antagonists and antiplatelet agents is proceeding at a rapid pace.

Concerns over the inability to achieve successful reperfusion consistently and prevent reocclusion also have been addressed using adjunctive coronary angioplasty. However, its role is still poorly defined, particularly in patients in whom reperfusion fails, after which "rescue" procedures intuitively seem important.

New developments toward improved efficacy and fibrin specificity of thrombolytic agents will hopefully overcome the limitations of currently available agents. It is theoretically possible that either tissue plasminogen activator or chimers will offer advantages that preclude the need for conjunctive therapy, while concomitantly reducing hemorrhagic risk.

A comprehensive approach to patient care demands that a risk to benefit perspective be undertaken. Thrombolytic therapy will likely remain the treatment of choice for patients with AMI. Extensive experience with thrombolytic agents has confirmed their safety and efficacy and has also uncovered some of their limitations. Thrombolytic therapy represents a significant stride forward in the treatment of AMI, and we have seen that its benefits clearly outweigh its risks. Additional investigation must be undertaken to assure continued growth and development of this important area.

Clinical Benefits of Thrombolytic Therapy in Acute Myocardial Infarction

Alan J. Tiefenbrunn, MD

The value of coronary artery reperfusion resulting from pharmacologically induced fibrinolysis in patients with evolving myocardial infarction has been rigorously evaluated. Improved left ventricular function and even more impressive improvements in survival rates have been demonstrated consistently in controlled studies. Benefit is related to the restoration of myocardial blood flow. Maximal benefit is achieved with early and sustained restoration of coronary artery patency. Benefits observed during initial hospitalization are sustained for at least 1 year in the majority of patients, even without subsequent mechanical revascularization. To date, analysis of subgroups has not identified a population of patients with evolving infarction that should routinely be excluded from consideration for thrombolysis.

As with many potent pharmacologic agents, activators of the fibrinolytic system are associated with a degree of risk whenever they are administered to a patient. Therefore, patients must be assessed carefully prior to initiating treatment, especially for potential bleeding hazards, and appropriate follow-up evaluation and concomitant therapy needs to be planned. However, given the overwhelming body of data now available regarding its benefits and relative safety, thrombolysis should be considered as conventional therapy for patients with acute evolving myocardial infarction (AMI).

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Pharmacologic activation of the human fibrinolytic system is accompanied by the possibility of bleeding. This and other risks will be thoroughly discussed elsewhere in this supplement. However, despite the potential risks, the clinical benefits of thrombolysis among patients with acute myocardial infarction (AMI) have been consistently documented over the last decade. This review will focus on evolving concepts and data supporting the widespread application of thrombolysis to patients presenting with AMI.

MECHANISM OF BENEFIT

It is evident from both laboratory and clinical studies that the benefits of thrombolytic therapy in AMI are conferred exclusively by restoration of patency of the infarct-related artery.[1]

This was demonstrated in the Western Washington trial of intracoronary streptokinase,[2] in which improved 1-year survival of 97.5% was observed only in the group of patients in whom patency had been documented angiographically. Those patients who received intracoronary streptokinase but did not have angiographic documentation of efficacy had a survival rate identical to the control group, 85%. Similarly, in the Thrombolysis in Myocardial Infarction (TIMI-I) study of intravenous streptokinase compared with intravenous recombinant tissue-type plasminogen activator (rt-PA),[3] the survival rate at 12 months in patients exhibiting reperfusion at 90 minutes was 91.9% compared with 85.2% in patients exhibiting persistent occlusion. Significance in this study ($p = 0.07$) was borderline because of its relatively small size. Patients without clinical or angiographic evidence of reocclusion at the time of hospital discharge had a 12-month survival rate of 96.2%. Further, improved survival correlated with coronary artery patency rather than with the thrombolytic agent employed. Similar correlations between early angiographic patency and 1-year survival were demonstrated in the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI-I) study of rt-PA with adjunctive angioplasty[4] and in the Duke Uni-

versity study of intravenous streptokinase and salvage angioplasty.[5]

The importance of sustained infarct-related artery patency was emphasized in a recent article by Ohman et al.[6] They presented the angiographic and mortality data for 797 patients studied in the TAMI series of trials in which patients with MI were treated with either intravenous rt-PA, urokinase, or both. A subset of 313 patients underwent adjunctive or salvage angioplasty following a 90-minute coronary arteriogram. Results of a repeat arteriogram performed within 7 days were also available. The in-hospital mortality rate for patients in whom early patency was achieved by thrombolysis and/or angioplasty and subsequently maintained at 7 days was 4.5% (Figure 1). In contrast, mortality among patients exhibiting early patency but experiencing reocclusion within 1 week was 11.0%, despite successful angioplasty or bypass surgery following reocclusion in 44%. Patients without angiographic documentation of reperfusion had an in-hospital mortality rate of 17.2%. Thus, maximum benefit is clearly associated with sustained patency.

MAGNITUDE OF BENEFIT

The degree of benefit that can be anticipated following successful lysis of an intracoronary thrombus depends on several factors, including the nature of the endpoint examined, time of evaluation, and the amount (both absolute and as a percentage) of myocardium that is salvaged. "Salvage" refers to the preservation of viability and contractility of myocardial cells that would have been irreversibly damaged in the absence of an intervention.

Mortality in controlled studies of thrombolysis is often expressed in the treatment group as a percentage decrease from the non-treatment group. Although such an analysis is likely valid for examining subgroups within a given study, application across studies is limited by different patient selection criteria and cotreatments. The ability to impact on mortality with a given therapeutic regimen will be influenced by the value of the control mortality and factors capable of influencing mortality. For example, it may be very difficult to demonstrate a reduction in mortality among patients with small inferior AMI in whom a very low baseline mortality rate is expected. Alternatively, a group of patients with left main occlusion will have a very poor prognosis despite receiving an otherwise effective therapeutic regimen.

Myocardial salvage will depend both on the amount of myocardium in jeopardy and the time interval from coronary artery occlusion to reperfusion. Although a patent infarct-related artery may have time-independent benefits that relate to improved healing, electrical stability, and availability of collateral flow,[7,8] maximum myocardial salvage and mortality reduction are clearly time-dependent.

The importance of time was demonstrated initially in animal studies of reperfusion, which showed that significant salvage of jeopardized myocardium did not occur after approximately 6 hours of

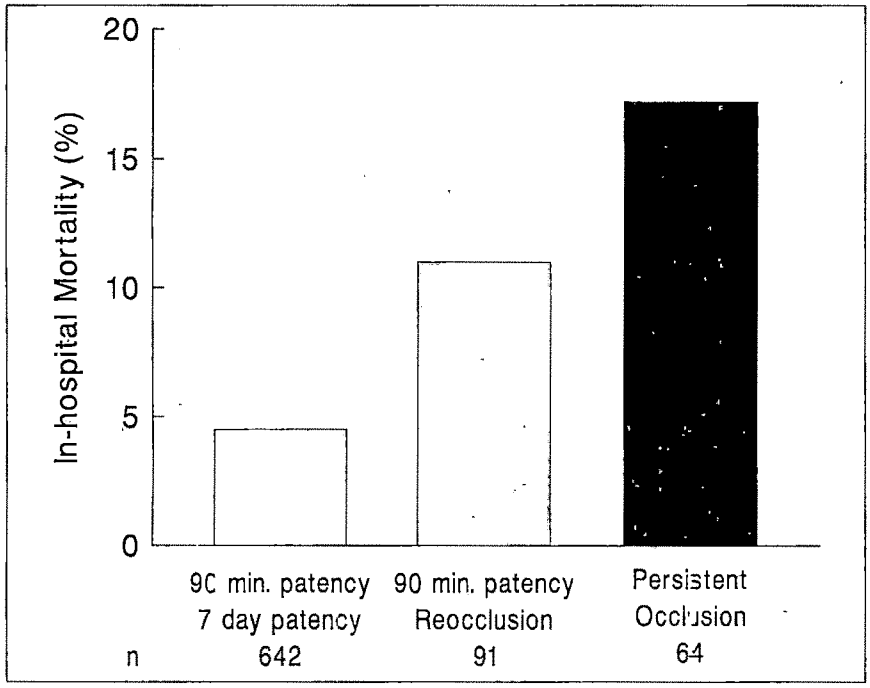


FIGURE 1. Graphic representation of the mortality data from the 4 TAMI studies reviewed by Ohman et al.[6] Patients exhibiting infarct artery patency at 90 minutes with continued patency at follow-up arteriography on day 7 had an in-hospital mortality rate of 4.5%. Patients with reocclusion within 7 days had an in-hospital mortality rate of 11%, even though 40 of these patients (38 with clinically manifested reocclusion, 2 with silent reocclusion) underwent successful angioplasty or bypass surgery. Patients with no demonstrable infarct artery reperfusion had an in-hospital mortality rate of 17.2%.

coronary artery obstruction.[9,10] It is especially important to note that the decrement in benefit of reperfusion over time is nonlinear; there is a very rapid decrement from approximately 30 to 120 minutes, followed by flattening of the curve. This phenomenon has also been observed in controlled clinical studies of thrombolysis in AMI. For instance, in the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI-1) trial of streptokinase, mortality was reduced by approximately 47% among patients treated with streptokinase within 1 hour compared with controls, whereas the mortality reduction was approximately 17% in those patients treated between 3 and 6 hours after symptom onset.[11] Similar decrements in mortality benefit were observed in the International Study of Infarct Survival (ISIS-2) trial of aspirin with or without streptokinase compared with placebo,[12] and in the European Cooperative Study Group (ECSG-V) trial of intravenous rt-PA compared with placebo.[13] Although the ISIS-2 study also demonstrated a small but significant mortality benefit in patients treated 6 or more hours after symptom onset, these data are somewhat difficult to interpret given the lack of strict electrocardiographic entry criteria for this study.

DURATION OF BENEFIT

Most studies have reported primarily early or in-hospital mortality, generally at 2–6 weeks following the acute event. Although this is partially related to the practical aspects of obtaining complete follow-up data, such reporting is considered valid since: (1) mortality associated with AMI tends to occur early (approximately 50% in the first 24 hours in both the TIMI-IIB[14] and GISSI-2/International rt-PA/Streptokinase Mortality Study trials[15,16]); (2) reocclusion on unstable plaques tends to occur early (approximately 50% of clinically manifested reocclusion was within 24 hours and 75% was within 72 hours in the TAMI studies[6]); and (3) controlled studies such as GISSI-1 with late follow-up data available demonstrate parallel survival curves following hospital discharge for treatment and control groups for at least 1 year.[17] Similarly, survival curves in the TIMI-IIB study remained parallel for 1 year, even though revascularization procedures were performed approximately 2.5 times more frequently during the first 6 weeks in patients randomized to the "aggressive" management group.

Thus, the benefits of early thrombolytic therapy persist for most patients. Reocclusion rates in patients treated with aspirin and intravenous heparin run approximately 12%, with clinically evident reocclusion (reinfarction) occurring in about one half of those exhibiting angiographic reocclusion.[6,14] Patients with reocclusion may be treated conservatively, retreated with a thrombolytic agent[18,19] or referred for angiography and possible mechanical revascularization.[6]

LEFT VENTRICULAR FUNCTION BENEFIT

Since myocardial salvage is a stated goal for restoring infarct artery patency, left ventricular function is a natural endpoint to be evaluated in trials of thrombolytic therapy.[20] Improved left ventricular function has been demonstrated in controlled trials of both streptokinase and rt-PA. In a study of intravenous streptokinase from Auckland,[21] patients evaluated by left ventriculography 3 weeks following infarction were found to have a mean ejection fraction of 59% with thrombolysis compared with 53% without. In a study of intravenous rt-PA from Johns Hopkins,[22] ejection fraction 10 days after infarction as assessed by radionuclide ventriculography was 53% in treated patients compared with 46% in those not receiving rt-PA. The Australian Thrombolysis in Acute Coronary Occlusion[23] study evaluated left ventricular function by both radiographic and radionuclide ventriculography. Patients treated with rt-PA had a mean global ejection fraction of 61% at 21 days compared with a value of 54% in control patients as assessed by contrast ventriculography. Radionuclide ventriculography demonstrated a 52% mean ejection fraction in treated patients versus 48% in controls.

Although significant differences in left ventricular function have been demonstrated for both anterior and inferior AMI,[21–23] more impressive and easily demonstrable differences are seen in patients with the former. For instance, in the Western Washington trial of intravenous streptokinase,[24] radionuclide ventriculograms performed 8 weeks following treatment demonstrated an ejection fraction of 48% in patients with anterior AMI treated within 3 hours compared with 38% in control subjects. Similarly, in the Australian National Study of Intravenous rt-PA,[25] patients with anterior AMI had a mean ejection fraction of 52.7% as assessed by angiography 3 weeks following treatment with rt-PA compared with 40.0% among control patients.

Although individual patients have demonstrated dramatic improvement in left ventricular function following successful thrombolysis and statistically significant improvements have been demonstrated in many controlled studies, the overall

magnitude of apparent benefit as assessed by global left ventricular function has generally been modest. This relates in part to the endpoint itself, which is dependent on loading conditions, the status of the noninfarct region as well as the infarcted area, diastolic compliance and level of neurohumoral stimulation.[1,20,26] In addition, contractile function does not return immediately following successful reperfusion, with days or even weeks often required before recovery is complete. There may also be methodologic problems that make interpretation of data difficult. For instance, late diagnostic studies cannot be performed in patients who do not survive, and they may not be completed in other patients initially enrolled in the study. Survival of patients with very low ejection fractions who likely would have succumbed without intervention may "dilute" the overall results and lower the average ejection fraction of the group.[27] Further, ejection fraction alone is not the sole determinate of prognosis; left ventricular size and the status of both the infarct- and noninfarct-related vessels may also be important. Thus, there is often a disparity between the relatively modest impact of thrombolysis on left ventricular function compared with the more impressive gains that have been observed in assessment of mortality.

MORTALITY BENEFIT

The first large, randomized, controlled study assessing the impact of thrombolysis on mortality in patients with AMI was GISSI-1.[11] In this study, 11,806 patients were randomized to either intravenous streptokinase or standard therapy. Patients were enrolled up to 12 hours after symptom onset. The overall 3-week mortality was significantly lower (10.7%) in treated patients compared with the control group (13.0%), an overall reduction of approximately 18%. As already mentioned, mortality reduction was most dramatic in those patients treated within 1 hour, approaching 50%.

The ISIS-2 trial[12] randomized 17,187 patients to either streptokinase or placebo, with a secondary randomization to aspirin or placebo. Patients were enrolled up to 24 hours after symptom onset. The 30-day mortality in patients receiving placebo was 13.2%. Mortality was significantly reduced to 10.4% in patients treated with streptokinase alone and to 10.7% in those treated with aspirin. Patients receiving both streptokinase and aspirin had the lowest mortality rate, 8.0%, a 39% reduction compared with control subjects. As in the GISSI-1 trial, the most dramatic reduction in mortality was in patients treated within the first hour, 56% for those receiving the combination of aspirin and streptokinase.

Anisoylated plasminogen streptokinase activator complex (APSAC) has also been shown to reduce mortality in a large randomized trial. Approximately 1,000 patients were randomized within 6 hours of symptom onset in the APSAC Intervention Mortality Study (AIMS) trial.[28] Mortality at 30 days was 6.4% in patients treated with APSAC compared with 12.2% in the control group.

The Anglo-Scandinavian Study of Early Thrombolysis (ASSET)[29] was a study of >5,000 patients randomized within 5 hours of symptom onset to receive either rt-PA or placebo. Mortality at 30 days was 7.2% in rt-PA–treated patients compared with 9.8% in control patients. It is of note that patients in this trial were not treated routinely with aspirin and that a conjunctive heparin infusion was continued for only 24 hours.

The European Cooperative Study Group[13] reported the results of a smaller placebo-controlled mortality trial of rt-PA: 721 patients were randomized within 5 hours of symptom onset. Patients were treated aggressively with aspirin and intravenous heparin. Despite a low control group mortality, the mortality rate at 2 weeks for those patients treated with rt-PA was 3.7%, a 46% reduction.

A recent review of mortality data from 25 studies of patients treated with either placebo, a first-generation thrombolytic drug (streptokinase, urokinase, or APSAC) or a second-generation drug (rt-PA or single-chain urokinase plasminogen activator) demonstrated an overall early mortality rate of 9.4% in 16,824 patients treated with first-generation drugs compared with a mortality rate of 5.6% in 8,501 patients treated with second-generation agents.[1] Placebo group mortality in these trials was 11.8% in 18,679 patients. Although these trials cannot be directly compared due to differing patient selection criteria, timing of mortality reporting and adjunctive and conjunctive regimens, the results demonstrate the consistent mortality benefit of thrombolysis, and suggest, moreover, further improvement in mortality in patients treated with second-generation fibrinolytic drugs, which induce thrombolysis more rapidly.[30] This analysis does not include the more recently reported direct comparison studies, GISSI-2,[15] the rt-PA/Streptokinase International Mortality trial,[16] and the ISIS-3 preliminary results, which were reported at the American College of Cardiology meeting in March 1991. It is of interest that these large multicenter trials reported early mortality rates comparable to the composite mortality rate of 9.4% for first-genera-

tion drugs; the overall 2-week mortality rate for the GISSI-2/International rt-PA/Streptokinase Mortality Study of rt-PA (alteplase) or streptokinase was 8.7%, the overall 5-week mortality rate for the ISIS-3 trial in which patients were treated with streptokinase, APSAC, or rt-PA (duteplase) was 10.5%. A more favorable mortality rate was not observed with alteplase or duteplase in these latter trials. However, these studies did not employ intravenous heparin, which likely mitigated the potential benefits of earlier reperfusion with the second-generation agents.

Inferior wall myocardial infarction: Some physicians have questioned whether aggressive treatment with thrombolysis or angioplasty is warranted in patients with inferior AMI, given the potential economic cost and medical risk. On average, the prognosis following an uncomplicated inferior AMI is good; these infarctions tend to be smaller, damage may be distributed between the two ventricles, and permanent conduction system problems are infrequent. However, controlled studies have demonstrated consistently a survival benefit in patients with inferior AMI receiving a thrombolytic agent. Grines and DeMaria[31] summarized the mortality data available for this patient subset from 9 controlled studies. Despite a relatively low control mortality rate of 8.7%, the mortality rate for AMI patients treated with thrombolytic therapy was 6.8%, a highly significant difference for the total population of 6,008 patients. Although the magnitude of benefit may not be as large for patients with inferior AMI as for those with anterior AMI, this finding relates to the overall size of the infarct rather than to its location per se.[32] Unfortunately, one cannot always predict how large an infarct will ultimately be, particularly when a quick decision has to be made regarding whether thrombolytic therapy should be instituted. Although not yet documented, late mortality may also be influenced favorably by successful treatment of an inferior AMI. Prognosis following a second AMI, i.e., in a second vascular distribution, may be affected both by the availability of collateral vessels and whatever myocardial salvage occurred in association with reperfusion of the inferior wall. Although an inferior location may be a consideration in the presence of relative contraindications, it should not in and of itself influence the decision to treat.[31–33] Clearly, patients with a large inferior AMI, as indicated by electrocardiographic criteria[34] or hemodynamic instability resulting from either right or left ventricular dysfunction, should be considered for aggressive therapy.

Advanced age: As initial pilot studies of thrombolysis were expanded to large, multicenter trials, older patients were often excluded by protocols in the hope of minimizing the risk of applying this new therapeutic modality. There was concern that the risk of complications, especially bleeding and stroke, would be increased in older individuals, and therefore an age of 75 years was often used as a cutoff point. However, as the experience with thrombolysis broadened, and several predominantly European studies included older patients, it became clear that although the risk of thrombolysis did increase with increasing age, the risk was outweighed by the potential benefit. This is true, at least in part, because AMI-related mortality increases with advancing age.[35] In a review of 5 studies that included older patients, Grines and DeMaria[31] observed a significantly lower mortality rate of 17.9% in older patients receiving thrombolytics when compared with patients managed without thrombolytic therapy, in whom the mortality rate was 22.1%. To date, no controlled study has demonstrated an increased mortality in older patients receiving thrombolytic therapy. Indeed, in the ISIS-2 study, the greatest decrements in mortality with treatment were observed in older patients. Thus, although advanced age may be associated with a higher incidence of relative contraindications, it should not by itself be considered a contraindication to thrombolytic therapy.

Late treatment: Whether patients presenting >6 hours after onset of AMI benefit from thrombolytic therapy remains controversial. Although significant myocardial salvage is unlikely to occur following 6 hours of persistent coronary artery occlusion,[9,10] patients are more complex than experimental models. Identifying the onset of occlusion is often imprecise, and moreover, thrombotic obstruction may be incomplete or intermittent, or collateral flow may be recruited and greatly prolong the time period during which myocardial damage remains potentially reversible. In addition, time-independent benefits of reperfusion, i.e., those that do not depend directly on myocardial salvage, may also exist. Interest in late treatment was stimulated by ISIS-2, which reported an improved mortality in patients treated with streptokinase 5–24 hours after symptom onset. The design of ISIS-2 was itself influenced by the observed benefit of late treatment (7–24 hours) identified in a meta-analysis of 33 earlier trials.[36]

The preliminary results of the Estudio Multicentrico Estreptoquinasa Republicas de America del Sur (EMERAS) trial were presented at the Ameri-

can College of Cardiology meeting in March of 1991. In this study, approximately 3,500 patients presenting 7–24 hours after AMI were randomized to receive either streptokinase or placebo. Complication rates in patients receiving streptokinase were relatively high, with an intracranial hemorrhage rate of 0.9% and a 0.4% incidence of anaphylactic shock. There was no significant difference in early mortality. However, heparin was not used in this study and thus some of the potential benefit of late reperfusion with streptokinase may have been lost due to reocclusion. In addition, it is known that streptokinase is less effective in dissolving older clots.[37] Further, one would not necessarily expect late reperfusion with minimal myocardial salvage to result in a dramatic difference in early mortality; many of the time-independent benefits of a patent infarct vessel, such as improved electrical stability and availability of collateral vessels, may not influence mortality for many months or years.

Additional studies are underway, including the Late Assessment of Thrombolytic Efficacy (LATE) study, which will randomize approximately 5,000 patients between intravenous rt-PA or placebo 6–24 hours after the onset of AMI. Data should also be forthcoming from the ISIS-3 trial regarding the results of randomization of patients who presented between 6 and 24 hours. In addition, the TAMI investigators have ongoing randomized trials to evaluate the effects of rt-PA or angioplasty in AMI patients treated >6 hours from symptom onset.[38]

Although uniform treatment with a thrombolytic agent beyond 6 hours cannot be recommended based on currently available data, this cutoff point should be regarded as a guideline rather than as an abrupt demarcation. Certainly, patients presenting beyond 6 hours with either "stuttering" symptoms, i.e., ongoing pain suggesting continuing or recurrent ischemia, or a large AMI with hemodynamic compromise should still be considered for thrombolytic therapy or urgent angiographic evaluation.

Nondiagnostic electrocardiogram: Patients presenting with symptoms suggestive of AMI but without significant ST-segment elevation present another dilemma. Patients enrolled in the ASSET study of rt-PA[29] and the ISIS-2 study of streptokinase[12] with normal electrocardiograms did not demonstrate a mortality benefit with thrombolytic therapy. Further, in each study the mortality for control patients was very low. Therefore, routine treatment of patients presenting with a completely normal electrocardiogram cannot be recommended.[31]

Patients with ST-segment depression were enrolled in both the GISSI-1 and ISIS-2 studies of streptokinase. In this patient subset, neither study demonstrated a survival benefit with thrombolytic therapy. However, both treated and control mortality rates were remarkably high, averaging 18.6% for a total of 1,588 patients. As pointed out by Grines and DeMaria,[31] this finding may reflect a selection bias of sicker patients manifesting only ST-segment depression. It has been suggested that patients with extensive ST-segment depression and hemodynamic compromise should be considered for thrombolytic treatment if urgent cardiac catheterization is not feasible.[32] Further investigation of this area is warranted.

ST-segment elevation cannot be assessed reliably in patients with complete left bundle-branch block. Yet, the prognosis for these patients is often poor. In the ISIS-2 trial, 827 patients with complete left bundle-branch block were enrolled. Control mortality was 27.7%, in contrast to 19.8% in patients treated with streptokinase. The overall mortality rate was 14% in patients receiving both streptokinase and aspirin. These data suggest that patients with a clinically convincing picture of AMI with a left bundle-branch block pattern should be considered for thrombolysis.[31]

Prior bypass surgery: Patients with prior coronary artery bypass grafting were excluded from early studies of thrombolysis to maximize the uniformity of the patient population. However, remote bypass surgery should not be considered a contraindication to lytic therapy. Although graft occlusion is more likely to occur than native vessel occlusion, this distinction is difficult to make on the basis of clinical information.[39] Graft thrombosis is relatively resistant to thrombolysis due to the large thrombus mass and poor flow through the graft resulting in limited delivery of the lytic agent. Thus, these patients might be considered for early angiography after thrombolytic therapy is initiated, especially if a large myocardial infarction appears to be evolving.

Previous AMI: Prior AMI was also an early exclusion criterion in the interest of assuring uniformity of patient populations. Subsequent studies have included patients with previous AMI: 15% of patients in the GISSI-1 trial,[11] 14% of patients in the TIMI-II study,[14] and 17% of patients in the GISSI-2/International rt-PA/Streptokinase Mortality Study had a history of previous infarction.[15,16] Mortality was 18% in patients with previous AMI

in the GISSI-1 study, compared with 7% in those without prior AMI, and it was not affected by therapy with streptokinase.[40] In contrast, patients with a previous AMI were shown to benefit from active therapy in ISIS-2.[12] Although the prognosis is worse and the impact of thrombolysis may be less in these patients, they should not be excluded from consideration for thrombolytic therapy.

MAXIMIZING BENEFIT

Efforts to maximize the potential benefits of thrombolysis include measures to treat patients more promptly, maximize early patency rates, reduce reocclusion rates, and enhance the benefits of reperfusion at the level of the myocardial cell.

Lytic regimens: Increasing the intravenous dose of streptokinase above 1.5×10^6 U does not appear to increase efficacy.[41] Although short-term, weight-adjusted, high-dose rt-PA has been investigated and appears to improve early patency rates,[42] there is general reluctance to employ an increased dose in the average sized patient in view of the excess intracranial bleeding that was observed in patients receiving rt-PA, 150 mg over 6 hours, in the TIMI trial.[14] However, accelerated administration of rt-PA with infusion of the usual 100 mg dose over 90 minutes has been demonstrated to produce patency rates as high as 90% at a 90-minute endpoint.[43,44] The t-PA versus APSAC Patency Study (TAPS), performed in Europe and reported at the American College of Cardiology meeting in March 1991, found a very low 4-week mortality, 2.4% of 199 rt-PA–treated patients, associated with an early patency rate of 85% at 90 minutes, using an accelerated rt-PA regimen combined with conjunctive aspirin and intravenous heparin. To date, an insufficient number of patients treated with accelerated regimens has been reported to confirm the safety and overall efficacy of this approach.

Combination regimens have also been evaluated but have not demonstrated synergy in increasing early patency.[45–48] However, in the TAMI-V study of rt-PA combined with urokinase, reocclusion rates were remarkably low.[49] The ongoing Global Utilization of Streptokinase and rt-PA for Occluded Coronary Arteries (GUSTO) trial is evaluating the mortality results in a large number of patients randomized to accelerated, weight-adjusted rt-PA or a combination of rt-PA and streptokinase therapy, compared with conventional streptokinase administration.

Conjunctive therapy: Both antiplatelet and antithrombin treatment are important in maintaining lytic-induced coronary artery patency. Survival in the ISIS-2 trial was increased by aspirin or streptokinase alone, but the lowest mortality was clearly associated with the combination of these two agents.[12] Heparin has been demonstrated in both noncomparative and comparative trials to improve outcome following thrombolysis.[1,50] Although heparin is important in patients treated with streptokinase, early institution of adequate heparin is vital in patients receiving rt-PA because of its short serum half-life and lack of systemic anticoagulant effects.[51,52] Heparin is usually continued for several days or until the time of cardiac catheterization if early angiography is planned, although a recent study suggests that it is the first 24 hours of heparin therapy that is most important.[53] The topic of anticoagulation and platelet inhibition is discussed extensively by Dr. Becker elsewhere in this supplement.

Adjunctive pharmacologic therapy: Numerous pharmacologic approaches had been suggested for maximizing the benefits of reperfusion, including α- or β-adrenergic blockade, calcium channel inhibition, free radical scavengers, and anti-inflammatory agents.[1] The only treatment studied in a significant number of patients is intravenous metoprolol, which was evaluated in patients enrolled in the TIMI-IIB trial who did not have a contraindication to β blockade.[54] Although neither overall mortality nor resting global ejection fraction at hospital discharge was affected, the incidence of recurrent nonfatal AMI was significantly reduced from 5.1% to 2.7%. The "low-risk" patients in this study had a 0% mortality rate when receiving intravenous metoprolol, compared with a mortality rate of 2.8% in the subgroup receiving deferred oral β blockade. It is also of interest that there was no intracranial bleeding in the patients treated with 100 mg rt-PA and intravenous metoprolol.[55] These trends suggest a role for early intravenous β blockade in patients being treated with a thrombolytic agent, as well as in those who are managed without thrombolysis.

Adjunctive angioplasty: Emergency cardiac catheterization of patients receiving thrombolytic therapy with subsequent angioplasty has been evaluated in several studies.[56–58] Dilation of vessels in which patency has been restored by thrombolysis has no proven benefit and may in fact be detrimental. In addition, reocclusion rates are not decreased and complication rates are relatively high. Rescue or salvage angioplasty of vessels that remain occluded following thrombolytic therapy may have a clinical role. Although success rates are relatively low and reocclusion rates are relatively

high in this selected group of patients, prognosis may be improved with successful restoration of patency.[59,60]

Elective angioplasty on a routine basis in patients treated with a thrombolytic agent has not been demonstrated to influence either mortality or reinfarction rates.[14] This was demonstrated both in the randomized portion of the TIMI-IIB study and in patients randomized to the conservative strategy but who subsequently underwent revascularization procedures.[61] Thus, based on the currently available data, revascularization should be reserved for patients experiencing reocclusion, recurrent ischemia, or hemodynamic instability. The role of mechanical revascularization is discussed thoroughly by Drs. Muller and Topol elsewhere in this supplement.

In conclusion, thrombolytic therapy in patients with AMI improves left ventricular function, decreases morbidity, and reduces mortality. Controlled trials demonstrate mortality reductions on the order of 20–50%, with the most dramatic results in patients treated early. The in-hospital mortality reduction is sustained over time, even in the absence of subsequent mechanical revascularization. Benefit is confined, however, to those patients in whom patency of the infarct-related artery is restored and is maximal with early, sustained reperfusion. Short-term intravenous heparin contributes to maintenance of patency, especially following rt-PA. Patients with inferior AMI as well as anterior AMI benefit, as do patients > 75 years of age who do not have specific contraindications. While additional data accumulate regarding patient selection, optimized lytic regimens, conjunctive therapy, and adjunctive therapy, sufficient data exist at this time to justify consideration of all patients presenting with evolving AMI for thrombolytic therapy.

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Clinical Risks of Thrombolytic Therapy

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Understanding the clinical risks of intravenous thrombolytic therapy is critical to appropriate patient selection. The major risks can be classified into 5 major categories: intracranial hemorrhage, systemic hemorrhage, immunologic complications, hypotension, and myocardial rupture. Although theoretical concern exists about thromboembolic complications, they rarely occur. Although cardiac rhythm disturbances are somewhat more likely to occur at the time of reperfusion, the clinical significance of "reperfusion arrhythmias" is minimal. Intracranial hemorrhage, the most devastating complication, occurs in 0.2–1% of patients treated with thrombolytic therapy. Factors associated with incremental risk are now being identified from large clinical trials. Systemic hemorrhage is uncommon in patients without major vascular punctures and seldom leads to serious adverse outcomes. Immunologic complications—including anaphylaxis, which is rare, and immune complex disease, which is more common—occur only with streptokinase or agents with a streptokinase moiety, including anistreplase (anisoylated plasminogen–streptokinase activator complex, APSAC). Hypotension, which can be managed easily in most patients, is also observed much more frequently with streptokinase and anistreplase. Myocardial rupture is increasingly being recognized as a possible complication of late thrombolysis.

A proper perspective on clinical risk can only be gained in the context of potential benefit of therapy. In many cases individual patients considered to be at highest risk for complications also stand to gain the most from treatment. Many of the questions raised by currently available data about bleeding risk are being addressed in the ongoing Global Utilization of t-PA and Streptokinase (GUSTO) Trial. A paradigm for considering this decision making problem is presented.

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The widespread acceptance of thrombolytic therapy has created an opportunity and a challenge to physicians treating patients with acute myocardial infarction (AMI). Results from clinical trials involving >100,000 patients leave no doubt that systemic administration of thrombolytic therapy can reduce the risk of dying by 10–50% compared with conservative therapy.[1] Evidence has also accumulated that preservation of left ventricular shape and function[1–3] leads to a reduction in congestive heart failure.[4] Unfortunately, the benefits to each individual patient must be tempered by the specific risk of complications for that patient. Since many of the large trials of thrombolytic therapy have not collected detailed information from the hospitalization, determination of accurate risk–benefit ratios has only recently become feasible.

The clinician at the bedside, presented with a patient experiencing AMI, must rapidly and accurately make a diagnosis and assess the likelihood of death or major complication with, and without, thrombolytic therapy. This assessment must increasingly take into account patient-specific characteristics. This section will review the current state of knowledge about the risks of thrombolytic therapy and the diagnosis and management of common complications. In addition, it will present a paradigm for evaluation of the individual patient.

BLEEDING

Since the goal of thrombolytic therapy is to lyse thrombi in a coronary artery, it is no surprise that the most common major complication of therapy is hemorrhage. The mechanism for bleeding is most likely lysis of a protective hemostatic plug, although depletion of clotting factors and loss of vascular integrity also often play a role.[5] Interpretation of clinical trials with regard to bleeding complications is difficult because of major differences in reporting of data and ancillary protocols. In the "mega-trials" designed to detect differences in mortality, detailed quality-controlled data about bleeding are absent, leading to underreporting of complications. Additionally, studies with mandatory early angiography and aggressive approaches

to revascularization have higher bleeding rates. Bleeding can be generally divided into 2 major categories, intracranial and systemic, since the risk factors and implications differ in many ways.

Intracranial bleeding: Intracranial bleeding is reviewed in detail in another article in this supplement.[6] Recent studies are beginning to clarify the incidence and risk factors for intracranial hemorrhage. Reported rates of intracranial hemorrhage are 0.2–1.0%.[6–11] Most studies with current dosing of thrombolytic agents have reported intracranial bleeding rates of 0.2–0.6%. Caution about these absolute rates is necessary, since the diagnosis of intracranial hemorrhage is very difficult to make in the absence of a definitive imaging procedure (computerized tomography or magnetic resonance imaging) or autopsy. In patients who die rapidly with sudden hypotension, it is often difficult to make a clinical differentiation of hypotension secondary to an intracranial event versus loss of consciousness secondary to hemodynamic compromise.

A major issue in the individualized patient risk assessment is whether the increased incidence of intracranial hemorrhage is offset by the decreased risk of embolic or thrombotic stroke with thrombolytic therapy. In fact, the major placebo-controlled trials of thrombolytic therapy have found little difference in total stroke rate between treated and control patients.[10,12–14] Historical studies have also demonstrated a total stroke rate of 1–3% during the hospitalization in patients with conservatively treated AMI.[15]

Both the mega-trials comparing recombinant tissue plasminogen activator (rt-PA) with streptokinase in AMI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico [GISSI-2][9]/International Mortality Study[16] and Third International Study on Infarct Survival [ISIS-3][17]) found a higher total stroke rate with rt-PA than with streptokinase, although the absolute magnitude of the difference was small (ISIS-3 used duteplase, a double-chain rt-PA). Combining the data from the 2 trials, 1.0% of patients treated with streptokinase were reported to have a stroke, compared with 1.3% of patients treated with rt-PA. In the GISSI-2/International Mortality Study, no significant difference was found in hemorrhagic stroke (0.3% with streptokinase vs 0.4% with rt-PA), although a substantial difference was found in "unclassified" strokes (0.3% vs 0.6%). In the preliminary report of ISIS-3, the major difference observed was in "definite or probable" intracranial bleeding (0.6% with rt-PA vs 0.3% with streptokinase). The temptation to ascribe the difference in stroke rates to the "classes" of agents (fibrin-specific vs nonspecific) is somewhat offset by the finding in ISIS-3 that the intracranial bleeding and total stroke rates were equally as high with anistreplase (anisoylated plasminogen–streptokinase activator complex, APSAC) as with rt-PA.

TABLE I Risk Factors for Intracranial Hemorrhage

Major (thrombolytic therapy absolutely contraindicated)
Known intracranial tumor
Prior neurosurgery
Recent stroke (within 6 months)
Recent head trauma (within 1 month)
Significant (substantial relative contraindication to thrombolytic therapy)
Acute severe hypertension
Remote stroke known not to be hemorrhagic
Recent transient ischemic attacks
Minor (increased risk of bleeding, but thrombolytic therapy not contraindicated)
Older age
Smaller body size
History of hypertension
Female gender

Adjunctive subcutaneous heparin therapy was found to be associated with an increase in the risk of intracranial hemorrhage in the GISSI 2/International Mortality Study and the ISIS-3 Trial. The magnitude of the increase was modest (0.4% without heparin vs 0.6% with heparin). Further, the total stroke rate was not different, presumably due to a reduction in thrombotic stroke with heparin.[18] The risk due to intravenous heparin is not known at this time, although the same trade-off between increased risk of hemorrhagic stroke and decreased risk of thrombotic stroke is likely to be present.

Major risk factors for intracranial bleeding can be divided into obvious risk factors that traditionally have comprised contraindications to therapy and the epidemiologic characteristics that have been found to signify higher risk (Table I). Interestingly, little is known about the actual risk in patients with common absolute contraindications, such as known intracranial tumor or recent stroke (within 6 months). Anecdotal experience, however, indicates that when patients with unsuspected intracranial metastasis have been treated, the intracranial bleeding rate has indeed been excessively high.

A point deserving emphasis is the critical importance of recent head trauma, especially in alcoholic patients or patients with inferior AMI experiencing either syncope or presyncope. In both situations the patient may not remember to impart information about the circumstances of the fall. Careful physical examination and questioning of witnesses

can provide important clues about the patient who, in fact, may have had significant head trauma.

A variety of risk factors have been identified in observational analyses of clinical trials.[6] More information will become available as details of the GISSI-2[9]/International Mortality Study[16] and ISIS-3[17] are reported. Acute hypertension, older age, and smaller body size have been found to be related to the risk of intracranial hemorrhage in most studies. Isolated studies have found higher risk in patients treated with calcium antagonists[6,19] and in smokers,[9] whereas acute treatment with β blockers has been found to be marginally beneficial in the Thrombolysis in Myocardial Infarction (TIMI) Trial,[19] but not in the GISSI-2[9]/International Mortality Study.[16]

Systemic bleeding: The risk of systemic hemorrhage with thrombolytic therapy varies dramatically among the published studies.[19–22] These differences reflect varying reporting and practice standards. In many small trials, detailed records are kept of each episode of bleeding and independent monitoring of the data guarantees full reporting of all complications. In the mega-trials, the data reporting systems have been dependent on volunteer effort without independent monitoring or funding for study coordinators at each site. Therefore, many modest bleeding episodes could have been missed. The larger trials have also included clinical centers with less aggressive approaches to percutaneous intervention, leading to a substantially lower rate of bleeding complications.

Several studies have now evaluated the patient-related risk factors for bleeding. The major risk factor is the use of invasive procedures such as cardiac catheterization, coronary angioplasty, intraaortic-balloon pumping and coronary artery bypass grafting.[21] In a summary of bleeding related to thrombolytic therapy, Fennerty and colleagues[23] reported that in protocols with systematic early cardiac catheterization the reported major bleeding rate was 12–15%, compared with 1% when catheterization was not part of the protocol.

Evidence that a careful approach to coronary angiography can reduce bleeding complications was developed in the Fifth Thrombolysis and Angioplasty in Acute Myocardial Infarction (TAMI-V) Trial[24] in which patients undergoing acute angiography within several hours of thrombolytic therapy administration had no higher bleeding risk than patients randomized to deferred angiography prior to hospital discharge. This strategy involves allowing only experienced angiographers to perform the procedure using small gauge catheters and avoiding puncture of the femoral vein unless necessary for hemodynamic monitoring or temporary pacemaker placement.

TABLE II Risk Factors for Systemic Bleeding

- **Major** (thrombolytic therapy absolutely contraindicated)
  - Major surgery or organ biopsy in past 6 weeks
  - Major trauma in past 6 weeks
  - Gastrointestinal or genitourinary bleeding in past 6 months
  - History of significant bleeding diathesis
- **Significant** (substantial relative contraindication to thrombolytic therapy)
  - Puncture of noncompressible vessel
  - Prolonged (> 10 minutes) cardiopulmonary resuscitation
- **Minor** (probable increased risk of bleeding, but thrombolytic therapy not contraindicated)
  - Diabetic retinopathy
  - Cardiopulmonary resuscitation < 10 minutes
  - Advanced age
  - Female gender
  - Small body mass

Intra-aortic balloon pumping poses a second level of bleeding risk. In a recent series, Ohman and colleagues[25] observed a mean decrease in hematocrit of 17±7% when an intra-aortic balloon pump was required versus 12±5% when a balloon pump was not used. The large diameter of the device inserted into the femoral artery unquestionably accounts for the major component of increased risk, although patients requiring intra-aortic balloon pumping are generally extremely ill; therefore, these same patients are at increased risk of bleeding from the multiple puncture sites often needed to provide optimal care.

As with intracranial bleeding, the actual risk associated with treatment in the case of a standard contraindication cannot be calculated, since conservative guidelines have been stressed as thrombolytic therapy has been adopted. These standard contraindications are listed in Table II.

A number of unclear areas exist with regard to the relative contraindications. The time frame in which prior surgery or trauma should be regarded as a contraindication remains unknown. Similar questions remain about the duration of time since an episode of gastrointestinal bleeding or the duration of treatment required for active ulcer disease.

Several potential risks have been overestimated in the past. Patients undergoing cardiopulmonary resuscitation early in the infarction stand to benefit from thrombolytic therapy and do not have a substantially increased risk.[26] Data are available only on patients treated < 10 minutes with cardiopulmonary resuscitation, however. Despite thousands of diabetic patients treated with thrombolytic therapy, cases of ophthalmic hemorrhage related to diabetic retinopathy have not been

reported. Although the exact proportion of these patients who had preexistent diabetic retinopathy is unknown, the risk is likely to be quite low.

After accounting for invasive punctures and contraindications, the remaining variability in risk of bleeding is difficult to quantify. Patient-related factors include older age,[21,27,28] female gender,[21] and smaller body mass.[21] These factors are relatively minor, however, and thus should *not* be considered absolute contraindications.

In the past, much concern was generated about creating a systemic fibrinolytic state. Many anticipated a hemorrhagic diathesis secondary to depletion of fibrinogen and other clotting factors. However, in multiple clinical trials comparing fibrin-specific and nonspecific agents[9,17,19,22,24,29] no substantial difference in overall bleeding risk has been encountered. In patients treated with rt-PA, however, a modestly increased risk of serious bleeding appears to occur in those with fibrinogen depletion and high titers of fibrin(ogen) degradation products.[19,22,30] Interestingly, this same coagulation profile seems to be associated with a lower risk of coronary reocclusion.[30]

Treating bleeding complications: A practical approach to bleeding complications has been described previously (Figure 1).[31] Bleeding should initially be classified according to severity, since life-threatening bleeding must be specifically treated as a medical emergency, whereas temporizing measures can be considered with more minor bleeding. When minor bleeding occurs from a vascular puncture site, simple manual compression for 20–30 minutes will usually suffice.

All patients given thrombolytic therapy should have their vital signs and neurologic status assessed frequently. Any focal change in neurologic function or sudden change in mental status should be considered to be the result of intracranial bleeding until proven otherwise. All of the following steps should be taken while an emergency head-imaging procedure is ordered to substantiate the diagnosis. If systemic bleeding leads to hemodynamic compromise (low cardiac output or persistent hypotension), a similar response should be undertaken in addition to immediate manual compression of the bleeding site.

After the clinician is satisfied that the bleeding is serious and will not stop with simple manual efforts, infusion of the thrombolytic agent should be discontinued. Heparin should also be discontinued and thought should be given to reversing the heparin effect with protamine, with 1 mg protamine for every 100 U of heparin given to the patient over the past 4 hours. The clinician should be aware that protamine can cause allergic reactions, especially in diabetic patients and in those with prior exposure to protamine. Anaphylaxis in up to 2% of patients has been reported in addition to hypotension and acute pulmonary hypertension.

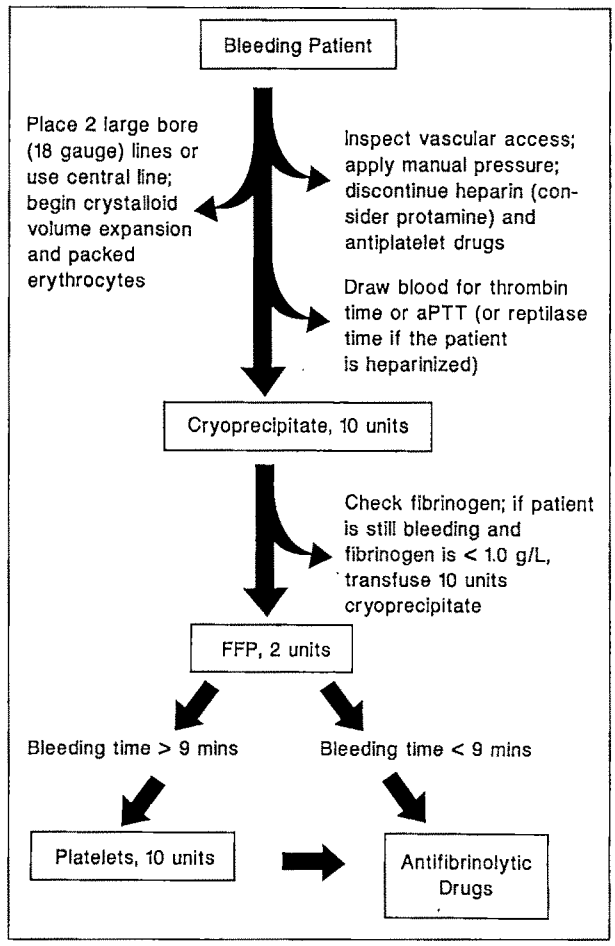


FIGURE 1. Management of bleeding after thrombolytic therapy. aPTT = activated partial thromboplastin time; FFP=fresh frozen plasma (Reprinted with permission from Ann Intern Med.[31])

Of course, aspirin should be discontinued, although this measure is often forgotten, since it has become part of the standard orders for patients with thrombolytic therapy. If the bleeding is immediately life-threatening, platelet transfusion should be given, since platelet function is affected by aspirin for days after dosing is stopped.

Blood product transfusion is a complicated issue. In past years, packed red blood cells were commonly transfused when the hematocrit fell to <30%, in order to maintain oxygen delivery to the heart and systemic tissues. Because of the small, but finite, risk of transmission of viral illnesses, the criterion for transfusion has become a hematocrit of 25%, unless severe hemodynamic compromise is present. Current estimates are that properly

screened blood carries a 1 in 40,000 chance per unit for transmitting the human immunodeficiency virus.[32] Multiple donor blood products, such as cryoprecipitate and platelets, carry an independent risk from each donor. Hepatitis and cytomegalovirus infection are even more prevalent.

When transfusion is needed to stop bleeding, cryoprecipitate (10 U) has been recommended as the first choice, since it has a large amount of fibrinogen and also contains significant amounts of Factor VIII. Cryoprecipitate is likely to be helpful only during or in the first few hours after thrombolytic drug infusion, since fibrinogen levels rebound after that point. If possible, the clinician should check the fibrinogen level when severe bleeding is encountered, to avoid unnecessary blood product transfusion in patients without a systemic fibrinolytic state. Fibrinogen levels must be obtained in a special preservative when the fibrinolytic agent is in the circulation, since in vitro fibrinogenolysis can artificially lower the measured fibrinogen level. For similar reasons, a repeat dose of cryoprecipitate may be needed when a significant amount of fibrinolytic agent remains in the circulation, since infused fibrinogen can also be destroyed.

Fresh frozen plasma may be used to replete clotting factors in patients with a profound lytic state and ongoing bleeding, with the usual dose being 2–4 U.

ϵ-Aminocaproic acid (Amicar) is an agent that actively counters the fibrinolytic effects of plasminogen activators. This agent, however, may produce refractory thrombosis and should be used only when other measures have failed to control bleeding. The risk of recurrent coronary thrombosis must always be weighed against the risk of bleeding. When intracranial bleeding occurs or the patient is experiencing any potentially life-threatening bleeding and has been known not to have reperfused, a dose of 5 g should be given as a loading dose, followed by an infusion of 0.5–1 g/hr until the bleeding subsides.

The patient with significant hemorrhage after thrombolytic therapy presents a substantial challenge to the clinician. Important decisions based on limited information must be made in a short period of time.

IMMUNOLOGIC COMPLICATIONS

The active components of both streptokinase and anistreplase are produced by group C β-hemolytic streptococci, leading to a significant rate of immunologic reactions. In contrast, the other currently available thrombolytic agents are human proteins, or derivatives of human proteins, and thus are not significantly antigenic. The allergic manifestations associated with the use of streptokinase and anistreplase can be divided into 2 groups. Acute anaphylaxis is unusual, but can be devastating, whereas delayed immune complex manifestations are more common, but generally less serious.

In the large trials reported to date, frank anaphylaxis has been reported in $<0.2\%$ of patients.[9,17] The diagnosis of anaphylaxis is difficult to make in the AMI setting, however, since hypotension from cardiogenic shock and bronchospasm from pulmonary edema are relatively common. Whether the incidence is underreported in patients who die of apparent cardiac causes remains uncertain. Although patients who survive anaphylaxis have high levels of streptokinase-specific immunoglobulin E (IgE),[33,34] prior treatment with steroids has not proven to be effective in preventing severe allergic reactions.[12]

When a patient recently treated with streptokinase or anistreplase develops bronchospasm and hypotension, a rapid decision must be made about whether the clinical deterioration has resulted from hemodynamic compromise or anaphylaxis. If anaphylaxis is thought to be present, large amounts of fluid should be given and the streptokinase infusion discontinued. Epinephrine (1:1,000) is given subcutaneously at a dose of 0.1–0.5 ml. Careful observation of airway integrity is essential.

In the days following streptokinase or anistreplase administration, a variety of allergic manifestations can become apparent Fever, arthralgias, and leukocytoclastic vasculitis can occur.[35] Renal failure occurs occasionally.[36] Interstitial pulmonary abnormalities have been encountered occasionally in the first several days after acute myocardial infarction in the absence of elevated pulmonary capillary wedge pressure. All of these findings are compatible with immune complex disease caused by IgG–streptokinase complexes.[33,37,38]

HYPOTENSION

When a patient with AMI experiences hypotension, multiple etiologies must be considered. Even in the absence of thrombolytic therapy, hypotension is common in the early hours of AMI because of pump dysfunction, relative volume depletion, and the Bezold-Jarisch reflex. Recent randomized trials have been useful in estimating the incremental relative risk of thrombolytic therapy. One contributing factor to hypotension is the conversion of high molecular weight kininogen, via a series of intermediate steps, to bradykinin, which occurs as

a by-product of the generation of plasmin in the systemic circulation. Bleeding and anaphylaxis must also be strongly considered in patients with hypotension after thrombolytic therapy.

Several carefully performed studies have demonstrated a significant decrease in systolic blood pressure in most patients given streptokinase. In the most carefully documented individual study, Lew and colleagues[39] demonstrated that an average decrease of 35 mm Hg occurred in streptokinase-treated patients and that 38% of patients transiently had a systolic blood pressure ≤ 90 mm Hg. The magnitude of this effect appears to be directly related to the rapidity of the infusion with streptokinase. Similar declines in systolic blood pressure have been documented with anistreplase.[11] In the GISSI-2[9]/International Mortality Study,[16] the rate of severe hypotension was 2.0% with rt-PA and 4.4% with streptokinase, whereas the preliminary ISIS-3 report[17] quoted a rate of 4.3% with rt-PA, 6.8% with streptokinase, and 7.2% with anistreplase.

Given these findings, one might assume that rt-PA would be preferable in patients with hypotension on presentation. In the GISSI-2/International Mortality Trial, however, the in-hospital mortality for patients with cardiogenic shock at baseline was 76% after rt-PA and only 64% after streptokinase therapy. The hypotension with streptokinase-related products is generally brief and responds rapidly to volume repletion by tilting or intravenous fluid administration. Our experience has been that in $<5\%$ of patients a brief vasopressor infusion is required.

MYOCARDIAL RUPTURE OR REPERFUSION INJURY

Many theoretical concerns have been raised that reperfusion, in restoring blood flow to ischemic or dying myocardium, could unleash a damaging process caused by production of toxic metabolites from dying tissue and clogging of the microcirculation by white blood cells. This process has been termed reperfusion injury. Two intriguing observations have raised the question of whether, despite the overall long-term benefit of reperfusion, the immediate process could be detrimental in individual patients. First, Honan and colleagues[40] demonstrated in a meta-analysis that the risk of myocardial rupture was decreased by early reperfusion, but that the risk increased as a function of time from symptom onset to thrombolytic administration. In fact, patients treated >12 hours from symptom onset had an increased risk of myocardial rupture compared with nontreated patients, presumably due to dissection of necrotic tissue to the epicardium by hemorrhagic infarction. Second, the GISSI-1[12] and ISIS-2[10] trials found that despite the dramatic reduction in in-hospital mortality with intravenous streptokinase, the mortality on the first day after treatment was actually higher in treated patients compared with control patients. Although this potential increase in risk must be recognized by the clinician, currently there is no preventive therapy and overall, in most patients treated within 12 hours of symptom onset, the potential for benefit outweighs the risk.[10,41,42]

THROMBOEMBOLIC COMPLICATIONS

Many reviews of contraindications to thrombolytic therapy have included valvular heart disease or left heart thrombi. Several reports[43,44] have now appeared describing cases in which systemic embolization has resulted from apparent lysis of intracardiac thrombi. Cholesterol emboli have also been observed after thrombolytic therapy.

REPERFUSION ARRHYTHMIAS

Arrhythmias are common in the first few hours of AMI. In animal experiments, sudden, early reperfusion frequently results in ventricular fibrillation or ventricular tachycardia.[45] The use of continuous ambulatory monitoring has demonstrated that, although ventricular arrhythmias are more common in patients with successful reperfusion, the difference is minor. Therefore, an arrhythmic event is not a reliable indicator of reperfusion.[46–48] Controlled trials have actually documented a reduction in the risk of ventricular fibrillation in patients treated with thrombolytic therapy.[12] Regardless of whether thrombolytic therapy is given, the patient with AMI should be carefully monitored in a setting where rapid defibrillation is available.

A continuing area of controversy is whether prophylactic measures can be taken to reduce lethal ventricular arrhythmias in the early hours of treatment. Meta-analyses of the use of lidocaine in the prethrombolytic era have failed to show a reduction in overall mortality, despite a reduction in ventricular fibrillation, because of a counterbalancing increase in asystole.[49,50] On the other hand, meta-analysis of the use of acute β blockade has shown a reduction in serious ventricular arrhythmias.[49] No large studies of either type of agent are available in patients treated with thrombolytic therapy. Further efforts are clearly needed in this

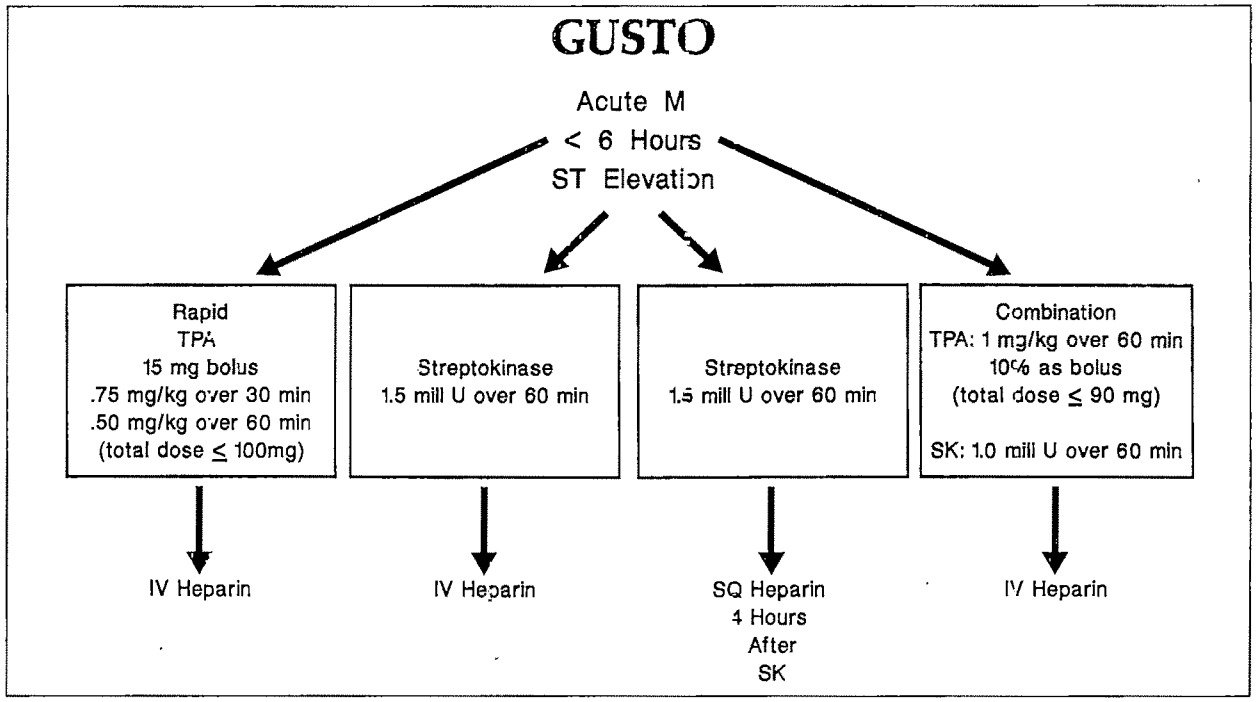


FIGURE 2. Global Utilization of Streptokinase and t-PA (GUSTO) Trial. IV = intravenous; MI = myocardial infarction; SK=streptokinase; SubQ = subcutaneous; t-PA = tissue plasminogen activator.

area to delineate successful strategies for prevention of ventricular arrhythmias.

RISK–BENEFIT

In general, the clinician must rapidly assess the balance between the reduction in morbidity afforded by coronary recanalization and the risk of life-threatening complications. In practical terms, the only common life-threatening problem attributable to the thrombolytic agent is bleeding. Based on current trial results, the magnitude of mortality reduction is inversely proportional to the time from symptom onset and directly proportional to the underlying risk without treatment. One factor known to be important in assessing the underlying risk without treatment is the size of the infarction as estimated from electrocardiographic and physical findings. The risk of intracranial and systemic bleeding is related to known contraindications (Tables I and II) and to age, gender, body size, and admission blood pressure.

In theory, these factors can be integrated into a regression equation to predict individual benefit and risk for each patient. Efforts are underway to combine data in a meta-analysis format so that a decision tool can be developed to provide point estimates of expected mortality and bleeding risk in the individual patient in real-time, similar to previous instruments for predicting the need for coronary care unit admission.[51] Such a tool could be programmed into a standard electrocardiographic machine.

ONGOING RESEARCH

Specific efforts are being made in the ongoing Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) Trial to provide additional information about risk. This large trial will randomize patients to 1 of 4 thrombolytic regimens, and in patients randomized to streptokinase, half will be treated with intravenous heparin and half with subcutaneous heparin (Figure 2). All patients with suspected stroke will have a diagnostic imaging study, and a detailed substudy is planned to evaluate factors associated with the occurrence and clinical outcome of hemorrhagic and nonhemorrhagic stroke. Survivors will have detailed assessment of quality of life in follow-up to 1 year. The major factors described above will be assessed in detail so that currently available predictive algorithms for bleeding and hypotension can be prospectively validated. The combination of very large patient samples and more detailed data collection should provide valuable new information for the practitioner.

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Ischemic Stroke and Intracranial Hemorrhage Following Thrombolytic Therapy for Acute Myocardial Infarction: A Risk–Benefit Analysis

Michael A. Sloan, MD, and Joel M. Gore, MD

Stroke is a potentially serious complication of acute myocardial infarction (AMI). In the prethrombolytic era, most strokes were attributed to cerebral embolism. On the basis of available information, the occurrence of stroke in the thrombolytic era appears to be less than in the prethrombolytic era. In the thrombolytic era, the occurrence of various forms of intracranial hemorrhage has increasingly been documented in addition to cerebral embolism, with intriguing features. In general, however, the delineation of specific stroke subtypes has been imprecise and must take into account factors that are unique to this setting. Age is a risk factor for both ischemic and hemorrhagic stroke. Potential risk factors for intracranial hemorrhage include hypertension, dosage of fibrinolytic agents, and prior neurologic disease. Potential causes of intracranial hemorrhage include combined fibrinolytic/adjunctive therapies, various cerebrovascular lesions, and head trauma. Existing data suggest that mortality related to stroke complicating AMI is on the decline as well. More research is needed in order to quantify precisely the occurrence and proportions of stroke subtypes, risk factors, and causes in order to define mechanisms and preventive measures.

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The occurrence of stroke has long been known to be a serious and infrequent complication of acute myocardial infarction (AMI). In the prethrombolytic era, stroke was reported to complicate the course of acute myocardial infarction in 1.7–3.2% of patients (Table I),[1–5] with a mortality rate of 54–61%.[1,2] A "typical" stroke occurred during the first week after AMI, although as many as 33% occurred within 24 hours of onset. The occurrence of stroke correlated with anterior or apical infarction,[1,2] large infarct size,[1] atrial arrhythmias,[2] cardiac pump failure or Killip class IV,[2] and history of previous stroke.[2] Most, if not all, strokes were attributed to cerebral embolism. The occurrence of intracranial hemorrhage was exceedingly rare. Anticoagulant therapy for AMI was complicated by central nervous system (CNS) hemorrhage in only 0.05–0.14% of treated patients.[5,6]

Echocardiographic studies of patients not receiving thrombolytic therapy demonstrate that left ventricular mural thrombi can occur in 28–34% of anterior AMIs and 0–1.5% of inferior AMIs.[7–9] Left ventricular thrombi typically occur during the first week after AMI,[9,10] although they may appear within 4 hours of onset[10,11] or after hospital discharge.[12] Thrombus formation is favored by extensive wall motion abnormalities such as anteroapical akinesia or dyskinesia and Killip class III or IV status.[13] An association with systemic and cerebral embolism has been observed.[7,8,13–15] Controlled studies have demonstrated an increased risk of embolism in AMI patients who harbor left ventricular mural thrombi.[16] The size and configuration of the left ventricular mural thrombi are important determinants of embolization. Risk factors for embolization include age > 68 years, pendulous or protruding thrombus, independent thrombus mobility,[12,16–19] and adjacent hyperkinesis.[19] Thrombus morphology may change spontaneously over weeks or months, with or without embolism.[20]

In the thrombolytic era, some changes in the

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TABLE I Occurrence of Stroke in the Prethrombolytic Era

Study	No.	No Anticoagulants		Anticoagulants	
		No.	%	No.	%
Medical Research Council[5]	1,427	715	2.5	712	1.1
Bronx Municipal Hospital[3]	1,136	391	2.3	745	1.7
VA Cooperative[4]	999	499	3.2	500	0.8
Thompson and Robinson[1]	783	586	1.7	197	1.5
Komrad et al[2]	740	740	2.4		
Total	5,085	2,931	2.4	2,154	1.3

characteristics of stroke have occurred. First, the reported occurrence rate of stroke complicating AMI in several large placebo-controlled (Table II),[21–31] comparative (Table III)[33–40] and many smaller trials[41–64] has decreased. This has been observed in trials using streptokinase,[21–26,36,37,41–52] anisoylated plasminogen–streptokinase activator complex (APSAC),[27,28] recombinant tissue-type plasminogen activator (rt-PA),[29–39,53–64] recombinant single-chain urokinase plasminogen activator (rscu-PA),[40,52] and various combination thrombolytic therapy regimens.[65] The incidence of stroke in treated groups is 0.5–2.5% (mean 1.06%) and in the control groups it is 0–1.0% (mean 0.81%) (Tables II, III).[21–40] Second, among the reported neurologic events, the distribution of stroke subtypes has shifted to include various forms of intracranial hemorrhage, such as parenchymatous intracerebral hemorrhage,[21–65] cerebral infarction with hemorrhagic transformation or hemorrhagic infarction,[25,38,43,44,56,61,66] and subarachnoid hemorrhage,[48,50,51] as well as subdural hematoma[31,33,38] and epidural hematoma (EDH).[67] Third, the location and timing of intracerebral hemorrhage complicating thrombolytic therapy for AMI are intriguing. Limited data[35,62,68] suggest that as many as 70% of these hemorrhages occur in the cerebral lobes (cortical and subcortical white matter) and they are frequently (33%) multiple.[35] This pattern is atypical for "hypertensive" hemorrhages (vide infra).

TABLE II Occurrence of Stroke in Placebo-Controlled Trials of Coronary Thrombolysis

Study (Agent)	Treatment		Control	
	No.	%	No.	%
1. GISSI[21,22] (SK)	63/5,860	1.1	54/5,852	0.9
2. ISAM[24,25] (SK)	5/859	0.6	0/882	0.0
3. ISIS-2[26] (SK)	61/8,592	0.7	57/8,595	0.8
Subtotal	129/15,311	0.84	121/15,329	0.79
1. ASSET[29,30] (rt-PA)	51/2,516	2.0*	34/2,495	1.4
2. ECSG[31] (rt-PA)	7/355	2.0	2/366	0.5
Subtotal	58/2,871	2.0	36/2,861	1.26
1. AIMS[27,28] (APSAC)	8/624	1.3	4/634	0.63
Total	195/18,806	1.04	151/18,824	0.86

APSAC = anisoylated plasminogen-streptokinase activator complex; ASSET = Anglo-Scandinavian Study of Early Thrombolysis; ECSG = European Cooperative Study Group; GISSI = Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico; ISAM = Intravenous Streptokinase in Acute Myocardial Infarction; ISIS-2 = Second International Study of Infarct Survival; rt-PA = recombinant tissue plasminogen activator; SK = streptokinase. *Includes TIAs.

Intracerebral hemorrhage has frequently been reported to occur during[58,59,68] and <24 hours after[22,23,25,26,29,38,66,68] infusion of the fibrinolytic agent. These observations have contributed to the ongoing controversy of the risk–benefit ratio of thrombolytic therapy, which thrombolytic agent is the most effective and safest treatment for AMI, and whether thrombolytic therapy should be used at all.[36,37,65,69]

In this review, we will assess the risk of stroke following thrombolytic therapy for AMI with respect to what is currently known about the occurrence of cerebral ischemia and hemorrhage in this setting. It is necessary first to become familiar with neurologic concepts of cerebrovascular disease in order to delineate the specific stroke subtypes and hemorrhagic phenomena in the brain. This will be accompanied by definitions for specific stroke types observed in the setting of thrombolytic therapy for AMI. Incidence rates and potential risk factors for cerebral ischemia and hemorrhage will be discussed. Finally, an assessment of the impact of thrombolytic therapy on prognosis for stroke after AMI will be made.

GENERAL ASPECTS OF STROKE DIAGNOSIS AND MANAGEMENT

Stroke may be defined as a focal neurologic deficit that lasts >24 hours, typically of sudden onset, due to a vascular lesion. Stroke is the most common cause of focal neurologic deficits in adults, but stroke is a complex and heterogeneous disorder. It must be noted that other brain disorders (e.g. tumor, abscess, subdural hematoma, multiple sclerosis) and some systemic conditions (hypoglycemia) may present in similar fashion. Historical features and findings on neurologic examination often provide enough information to enable the clinician to localize the site(s) of brain dysfunction and make a reasonable formulation of the mechanism or cause of the stroke. It is often difficult on clinical grounds to distinguish cerebral ischemia from hemorrhage, on the one hand, and thrombotic from embolic occlusions, on the other. Brain images (computed tomography and/or magnetic resonance imaging) are essential for determining the type, site, and size of the stroke while ancillary tests (cardiac, vascular, and laboratory) help to define specific vascular lesions and disease processes responsible for the stroke.[70,71] The frequen-

TABLE III Cerebrovascular Complications in Recent Large Coronary Thrombolysis Trials

Study	Stroke [n (%)]	ICH [n (%)]	CI [n (%)]	NS [n (%)]	SDH [n (%)]
A. Streptokinase[21,22,26,36,37,65,69]					
Subtotal*	208/24,848 (0.84)	45 (22)	55 (26)	108 (52)	
% of all patients		(0.18)	(0.22)	(0.43)	
B. Recombinant tissue plasminogen activator[29,33–38,65,68,69]					
Subtotal	267/20,408 (1.3)	95 (36)	103 (38)	64 (24)	5 (2)
% of all patients		(0.47)	(0.50)	(0.31)	(0.02)
C. Recombinant single chain urokinase plasminogen activator[40]					
Subtotal	15/1,032 (1.45)	8 (53)	7 (47)	—	—
% of all patients		(0.78)	(0.67)		
D. Total	490/46,288 (1.06)	148 (30)	165 (34)	172 (35)	5 (1)
% of all patients		(0.32)	(0.36)	(0.37)	(0.01)

*In the "subtotal" and "total" lines, the numbers in parentheses refer to the percentage of strokes in each subgroup. In the line, "% of all patients," the numbers in parentheses refer to the reported occurrence rate of each stroke subtype in the entire population treated with each agent or all agents. The total number of patients, strokes and percentages for stroke and stroke subtypes do not include results of the Third International Study of Infarct Survival (ISIS-3).
ICH = intracerebral hemorrhage; CI = ischemic cerebral infarction; NS = subtype not specified; SDH = subdural hematoma.

cies of well-defined specific stroke mechanisms or subtypes in diverse large populations[72–75] are depicted in Table IV. Once the stroke mechanism is established, subtype-specific medical or surgical therapy is administered.

COMMON STROKE SUBTYPES

Atherosclerosis: Atherosclerotic plaque formation leads to arterial narrowing or occlusion with resultant ischemic injury, either by artery-to-artery embolization or critical reduction in cerebral perfusion. The most common site is at the origin of the internal carotid artery, but clinically important disease may occur at various intracranial sites. On rare occasions, disease may affect superficial branches of the cerebral and cerebellar arteries.[71–76] Distinct clinical syndromes, either transient or persistent, occur with occlusive lesions of each particular vessel.[70,71,77–81] At times, apparent posterior circulation ischemia may be mimicked by anterior circulation occlusive disease.[82,83]

Angiographic and autopsy studies indicate that blacks and Japanese are more prone to develop intracranial atherosclerosis, and whites have more extracranial disease. Men have more extracranial disease and women (especially diabetics) may have more intracranial disease.[76]

Cardiogenic embolism: Embolic occlusion of any cerebral artery may originate from a wide variety of cardiovascular lesions[70,71,84,85] and, rarely, systemic (paradoxical) sources.[70,85,86] Diagnosis has been based on identification of a source of embolism and occurrence of so-called neurologic clinical criteria such as abrupt onset, loss of consciousness at onset, headache, seizures, evidence for deficits in multiple vascular territories, and embolization to other organs. The lack of validated neurologic criteria has hampered the clinical diagnosis and management of cardiogenic embolism.[87] If one defines patient groups based on the type of underlying cardiac condition, a number of clinical features are univariately associated with a strong likelihood of a cardiac source of embolism: abrupt onset, diminished level of consciousness at onset, systemic embolism, aphasia, hemispatial neglect, visual field deficits, and large (superficial and deep) infarctions on computed tomography scan.[88–91] However, recent studies indicate that patients with transient ischemic attacks (TIAs) referable to carotid stenosis commonly have a potential cardiac source of embolism, particularly (but not exclusively) in those patients with symptomatic heart disease.[91,92] Patients with single or multiple TIAs, TIAs in multiple territories, and multiple or silent cerebral infarcts on computed tomography scan may have carotid or cardiac lesions.[93] Since atherosclerosis may occur at sites other than the internal carotid artery, some patients may have concomitant cardiac and intracranial occlusive lesions responsible for TIA or stroke.

Small vessel disease (lacunae): Lacunar disease refers to occlusion of smaller (50–400 μm) intracranial penetrating arteries by segmental vessel wall disorganization ("lipohyalinosis"), at times associated with Charcot-Bouchard microaneu-

TABLE IV Distribution of Stroke Subtypes by Mechanism*

Stroke Subtype	Proportion (%)
Atherosclerotic, large artery	6–34
Embolic	14–31
Small vessel (lacunae)	11–19
Infarct, cause unknown	25–32
Intracerebral hemorrhage	10–14
Subarachnoid hemorrhage	6–13

*Data compiled from the Harvard Cooperative Stroke Registry,[69] Michael Reese Stroke Registry,[70,73] Pilot Stroke Data Bank,[74] and Main Phase Stroke Data Bank.[75]

rysms (vide infra).[70,71,94,95] The result is a small (usually <1.5 cm) infarction in the basal ganglia, internal capsule, thalamus, or pons. Early studies linked this vascular lesion to hypertension[94] but many cases occur in diabetics, smokers, and nonhypertensive persons.[95–97] Classic syndromes include pure motor hemiparesis, pure sensory stroke, clumsy hand-dysarthria, and ataxic hemiparesis, although a number of variants have been described.[70,71,95,96] These lesions are frequently invisible on computed tomography scans or, less likely, magnetic resonance imaging scans. Recent data suggest that lacunar syndromes may be caused by microatheroma, emboli, high-grade extracranial and intracranial stenosis, intracerebral hemorrhage, and nonvascular lesions.[70,95–99]

HEMORRHAGIC TRANSFORMATION OF ISCHEMIC CEREBRAL INFARCTION

Hemorrhagic transformation or conversion of a cerebral infarct (hemorrhagic infarction) occurs when red blood cells pass through damaged capillary and venular walls into the infarct. Hemorrhagic infarction is believed to occur either when there is early reperfusion into a damaged vascular bed with impaired autoregulation or because of development of collateral circulation.[100] It is known to occur sometimes when there is no recanalization, with or without acute hypertension.[100–102] This secondary bleeding may cause formation of petechiae of variable size.[100] If petechiae merge to form purpura or hematoma, a catabolic rupture or "infarct hemorrhage" may occur,[103] and a parenchymatous intracerebral hemorrhage will be detectable on computed tomography scan (Figure 1).[100] On occasion, blood may extend into the subarachnoid space or the ventricular system. Hemorrhagic transformation frequently occurs within 2–4 days after onset of cardioembolic stroke,[100,104] but may occur as early as the first day[105] or as late as 10–14 days after onset.[106,107]

The incidence of, and risk factors for, hemorrhagic infarction are difficult to evaluate because many studies describe both nonanticoagulated and anticoagulated patients.[106,108–114] In autopsy studies of small numbers of patients, cardioembolic strokes appear to have a higher propensity for hemorrhagic transformation (51–71% prevalence)[104,113] than nonembolic strokes (2–21% prevalence).[109,113] This may reflect ascertainment bias, since lethal infarcts are more often large with mass effect, brain herniation, or hemorrhagic infarction. It may also reflect treatment bias, since patients with nonembolic strokes are less frequently anticoagulated.[115] Of all patients with cardioembolic stroke in small clinical series, only 5% of computed tomography scans performed within 24 hours and 20% (range 8–62%) of computed tomography scans obtained within 1–2 weeks after stroke show hemorrhagic infarction,[108,110,115] often without worsening.[112] Hemorrhagic infarction in anticoagulated patients may be asymptomatic or symptomatic[109,112] and the latter has a reported mortality rate of 55%.[114] Recent studies indicate that hemorrhagic transformation of cardioembolic strokes appears more likely with age >70 years,[102] early initiation of therapeutic to excessive anticoagulation,[106,114] and hypertension[106,114] and may occur in similar frequency in different vascular territories.[101,102] The incidence of hemorrhagic infarction with clinical worsening in nonanticoagulated patients has not been established.[106,109,112,115]

Parenchymatous intracerebral hemorrhage: Intracerebral hemorrhage refers to primary bleeding within brain parenchyma. Classic studies suggested that hypertension was responsible for 72–94% of all intracerebral hemorrhage.[70,71,103] Hypertension may produce intracerebral hemorrhage by one mechanism or through interaction of several mechanisms.

First, chronic hypertension may damage cerebral arterioles and produce a number of microvascular lesions that may subsequently rupture. Charcot-Bouchard microaneurysms are saccular or fusiform dilations of small arteries 250–400 μm in diameter with degenerative changes in the adventitia.[116–121] These lesions may occur in any part of the brain, particularly those of elderly hypertensive patients. On occasion, a number of small hemorrhages may be found in the subcortical white matter, basal ganglia, and internal capsule.[118,120,121] Pseudoaneurysms[122] and fibrin ("bleeding") globes[121,123] are other microvascular lesions, the latter of which may be associated with an "avalanche" effect and hematoma enlargement. In spontaneous intracerebral hemorrhage cases, it is difficult to find these lesions in surgical specimens.[124,125]

Second, acute severe hypertension of sufficient degree may increase cerebral blood flow, particularly in the cerebellum, parietal gray matter, thalamus, striatum, and pons.[126] This may overcome cerebral autoregulation and lead to breakthrough perfusion, capillary rupture, and hemorrhage.[127]

Cold exposure,[127] use of sympathomimetic drugs (phenylpropanolamine[128] or cocaine[129,130]), dental pain,[127] and trigeminal nerve stimulation[127] are examples of situations in which intracerebral hemorrhage has been produced.

Third, a focal or diffuse increase in cerebral blood flow that occurs as a result of improved left ventricular function secondary to successful repair of a congenital cardiac obstruction (reperfusion) may lead to intracerebral hemorrhage.[127] This may also occur with reperfusion of ischemic or injured blood vessels and tissues in the brain.[127] Hemorrhagic infarction is but one example of this phenomenon.

Nonhypertensive causes of intracerebral hemorrhage include a variety of structural cerebrovascular lesions and systemic conditions. Arteriovenous malformations are uncommon vascular anomalies

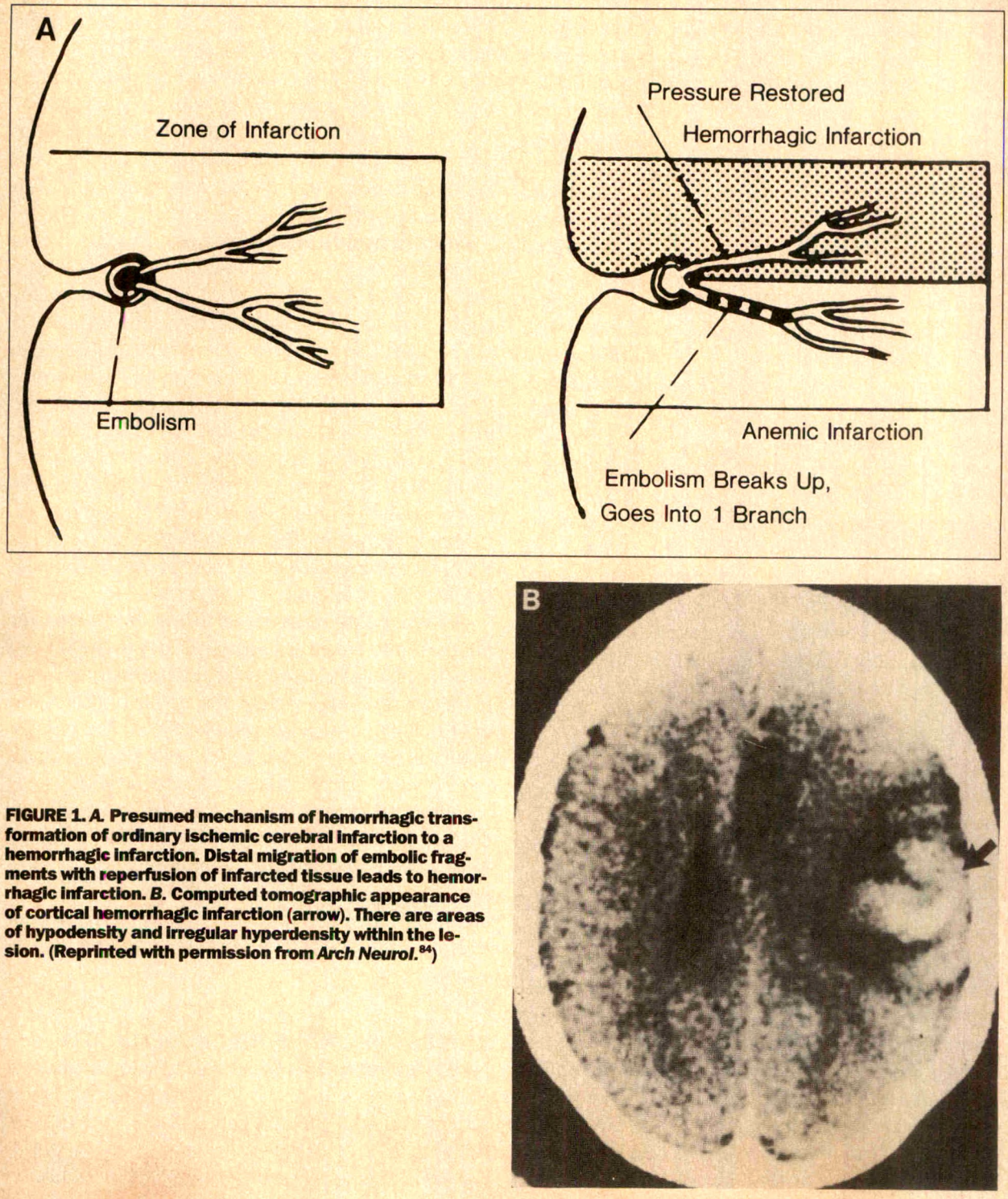


FIGURE 1. ***A.*** **Presumed mechanism of hemorrhagic transformation of ordinary ischemic cerebral infarction to a hemorrhagic infarction. Distal migration of embolic fragments with reperfusion of infarcted tissue leads to hemorrhagic infarction.** ***B.*** **Computed tomographic appearance of cortical hemorrhagic infarction (arrow). There are areas of hypodensity and irregular hyperdensity within the lesion. (Reprinted with permission from *Arch Neurol.*[84])**

that are in general composed of tangles of abnormally fragile arteries and veins, which are prone to rupture and produce intracerebral, subarachnoid, or intraventricular bleeding. Pathologic and magnetic resonance studies have demonstrated that these lesions can be complicated by subclinical episodes of thrombosis or bleeding.[131] On occasion, congenital "berry" aneurysms will rupture and blood will extend into brain parenchyma, especially the frontal and temporal lobes.[70,71,132,133] Cerebral amyloid angiopathy is recognized as an important cause of intracerebral hemorrhage in elderly people.[134,135] Amyloid angiopathy is characterized by an acellular thickening in the media and adventitia of small to medium sized arteries (including arterioles) and veins, particularly in the superficial cerebral cortex.[135] Ultrastructural studies have demonstrated petechial hemorrhages in cortical and subcortical regions[136] and the occasional presence of microaneurysms.[136,137] Blood vessels infiltrated by amyloid are leaky and brittle, unable to withstand trauma or blood pressure changes.[135] Intracerebral hemorrhage may also be associated with blood dyscrasia (leukemia),[133,134,138] anticoagulant therapy,[139] primary and metastatic brain tumors,[70,71,133,134] arteritis,[134] and use of illicit (cocaine,[129,130] amphetamines,[140] or phencyclidine[141]) and over-the-counter sympathomimetic (phenylpropanolamine[128]) drugs.

Intracerebral hemorrhage tends to occur in deep (putamen, thalamus, pons, cerebellum) and superficial (lobar, subcortical white matter) locations, depending on the etiology. Hypertensive intracerebral hemorrhage occurs in the putamen (35–40%), lobar subcortical white matter (25–35%), thalamus (12–20%), cerebellum (8–10%), and pons (5–8%).[70,71,135,136] However, many patients with hypertensive intracerebral hemorrhage do not have chronic hypertensive changes, such as left ventricular hypertrophy on electrocardiograms and hypertensive retinopathy. Recent clinical[142] and pathologic[142,143] studies have shown that only 45% of patients had prior histories of chronic hypertension, 15% had only transient hypertension, and 46% of autopsied patients had no clinical evidence of hypertensive cardiovascular or cerebrovascular disease. In normotensive patients, intracerebral hemorrhage reportedly occurs in the following proportions: lobar/subcortical white matter ($\leq$55%), deep ganglionic structures (putamen and thalamus) (35%), cerebellum (25%), and pons (10%).[133,134]

Intracerebral hemorrhage is generally believed to occur in a single location on one occasion, with a low recurrence rate.[70,71,133,144] However, multiple simultaneous hemorrhages may occur in 2–11%[138,145] of intracerebral hemorrhage cases. Previously recognized settings for multiple intracerebral hemorrhage include blood dyscrasia,[133,134,138] coagulopathy,[71] amyloid angiopathy,[136,146,147] neoplasms,[138] vasculitis,[138] venous sinus thrombosis,[138] and the use of cocaine[130] or phenylpropanolamine.[128]

Presenting features that are suggestive of intracerebral hemorrhage include headache, nausea, vomiting, depressed level of consciousness, and seizures, in addition to a specific focal neurologic deficit depending on the location.[70,71,133] Cerebral amyloid angiopathy-related intracerebral hemorrhage typically occurs in elderly, frequently demented, patients as single, multiple, or sequential subcortical lobar or cortical–lobar hemorrhages,[135] although many cases have been reported in the 6th and 7th decades.[146]

Subarachnoid hemorrhage: Subarachnoid hemorrhage is the least common stroke subtype and refers to arterial bleeding into the subarachnoid space. The most common nontraumatic causes of subarachnoid hemorrhage are ruptured congenital berry aneurysm or arteriovenous malformation. Other causes of subarachnoid hemorrhage include anticoagulant therapy,[70,71,148] blood dyscrasia,[149] primary and secondary central nervous system tumors,[143] arteritis,[70,71] and illicit[129,140] or over-the-counter sympathomimetic[128,134] drug use. Common presenting features include a severe headache, face or eye pain, photophobia, nausea, vomiting, loss of consciousness, and seizures.

Nonvascular causes of brain hemorrhage: Subdural and epidural hematomas may occur in association with significant or trivial head trauma, anticoagulant therapy, and a variety of systemic disorders but are rarely due to vascular lesions. Acute and chronic subdural hematomas are believed to grow by direct rebleeding.[150,151] Experimental[151] and clinical[152–155] studies suggest that the fibrinolytic system is activated in chronic subdural hematomas. As a result, the hematoma is defective and cannot provide effective local hemostasis. Any minor trauma can produce rebleeding or plasmatic effusion. Moreover, these events can lead to a self-perpetrating growth cycle and clinical symptoms.[151]

STROKE RISK IN THE THROMBOLYTIC ERA

Stroke rates and precision of diagnosis: The published rates of stroke in treated and untreated patients in placebo-controlled trials and treated patients in large comparative studies are shown in Tables II and III, respectively. The reported occur-

rence rate for stroke in placebo-controlled trials is 1.04% (range 0.6–2.0%) for treated patients and 0.86% (range 0–1.4%) for control subjects. In the Second International Study of Infarct Survival (ISIS-2),[26] there was an excess of early strokes (<24 hours) in the treatment groups compared with the control groups but fewer strokes after the early post-AMI period. In large comparative studies, the reported stroke occurrence rate was 0.84% (range 0.7–1.0%) in streptokinase patients, 1.3% (range 0.5–2.0%) in rt-PA patients, and 1.45% for rscu-PA patients. In the Third International Study of Infarct Survival (ISIS-3),[65,69] preliminary data suggest that 1.1% of streptokinase patients and 1.5% of duteplase patients had stroke ($p < 0.02$). "Probable cerebral hemorrhage" occurred in 0.3% of streptokinase patients, 0.7% of rt-PA patients, and 0.8% of APSAC patients ($p < 0.00001$). In 8 small studies (total of 760 patients) using combination thrombolytic therapy [rt-PA plus streptokinase or rt-PA plus urokinase], the reported intracerebral hemorrhage occurrence rate is 0.7% for rt-PA plus urokinase and 0.5% for rt-PA plus streptokinase.[69]

This apparent reduction in stroke risk may result from improved treatment of AMI patients in general and high-risk patients in particular. It may also be due to the exclusion of patients at high risk of stroke.[23,29,36–39,156] The wide variation in stroke rates could also be due to chance or, more likely, different intensity of the evaluation and reporting of stroke complications.[22,23,26,27,29,157–159]

For example, in ISIS-3,[65,69] the diagnosis of "probable cerebral hemorrhage" was based on the treating cardiologist's impression, without detailed data collection and analysis. In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2) and International Study Group trials,[36,37] the occurrence of stroke was significantly higher in the rt-PA group (1.3%) than in the streptokinase group (0.9%), for reasons that remain unclear. In these studies,[36,37,65,69] computed tomography scans were obtained in only 67% of patients.

Inspection of Table III indicates that the delineation of stroke subtypes in large comparative studies was uncertain or not specified in 35% (range 0–89%) of cases.[21,22,26,29,33–38,40,65,68,69] Description of ischemic stroke subtypes (i.e., atherosclerosis, cardiogenic embolism, lacuna, other) has not been performed. In large studies, the mean published intracerebral hemorrhage–occurrence rates after treatment with streptokinase, rt-PA, APSAC, and rscu-PA are 0.18%,[21–23,36,37] 0.47%,[29,33–38] 0.32%,[28] and 0.78%,[40] respectively. These rates are not readily comparable and may be due to ascertainment bias, since they are based on the frequency with which cerebral symptoms are investigated using brain images such as computed tomography or magnetic resonance imaging.[21–23,26,29,36,37,65,69]

As a complication of thrombolytic therapy for AMI, intracranial hemorrhage may be due to parenchymal intracerebral hemorrhage, hemorrhagic transformation of cerebral infarction, or subdural hematoma. Published criteria do exist to determine whether a hemorrhagic lesion on computed tomography scan is due to primary intracerebral hemorrhage or hemorrhagic infarction.[133,158] Primary hemorrhages are thought to be nonterritorial, compact, or confluent collections of blood that are seen on brain scans to have a homogeneous density and sharp edge, often with a surrounding mass effect occurring after several days (Figure 2). Hemorrhagic infarctions are strictly territorial and have mixed areas of hypodensity and hyperdensity with an indistinct edge and no significant mass effect at an early stage (Figure 1). The contribution

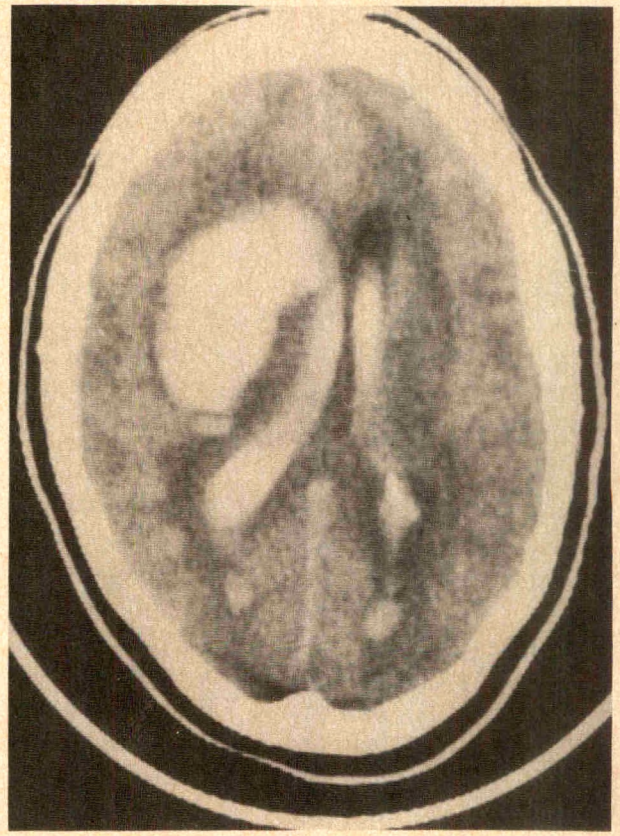


FIGURE 2. Computed tomographic appearance of a homogeneous right putamenal intracerebral hemorrhage with extension into the subcortical white matter and ventricular system. There is a thin rim of edema around the hematoma.

of thrombolytic therapy per se to the occurrence of hemorrhagic infarction over and above the effect of heparin and aspirin is not well defined.[115] In this setting, hemorrhagic infarction may be diagnosed if blood appears within an area of infarction on the first computed tomography scan or if the first scan is negative and hemorrhage is then seen in the presumed cerebral infarct location on a subsequent scan.[38] It may be difficult to distinguish a confluent hemorrhagic infarction from a primary intracerebral hemorrhage on computed tomography scan.[105,115,156] In the Thrombolysis in Myocardial Infarction (TIMI-II) trial,[38] 2 patients originally reported to have intracranial hemorrhage[66,159] have since been reclassified as hemorrhagic infarctions.[38,159,160] Of the 56 cerebrovascular complications in TIMI-II,[38] 8 of 29 (28%) ischemic cerebral infarcts were hemorrhagic. If these 8 are added to the 23 intracerebral hemorrhages, then up to 25% of "intracerebral hemorrhages" would be due to hemorrhagic infarctions. In larger study populations[22,23,26,27,29,36,37,65,69] it is thus possible that misclassification of hemorrhagic infarction as intracerebral hemorrhage may have occurred and that the rate of intracerebral hemorrhage is actually less than reported. Finally, subdural hematoma may be diagnosed if a high-density fluid collection is seen in the subdural space or if there is sulcal effacement and mass effect on brain images.

It is clear that the published rates for stroke and stroke subtypes following thrombolytic therapy for AMI are somewhat imprecise. Therefore, these rates should be considered as only estimates of the true rates. On the basis of current available data, putative risk factors for ischemic stroke and intracranial hemorrhage have been identified. The actual strength of the association between these factors and the occurrence of stroke, especially intracerebral hemorrhage, will need to be determined.

RISK OF ISCHEMIC CEREBRAL INFARCTION

The reported occurrence rate of ischemic stroke in large comparative studies is 0.36% (range 0.19–0.61%),[21,22,26,29,33–38,65,68,69] although the relatively large proportion of strokes of uncertain or unspecified type (0.37%) may increase the rate to as high as 0.73% (Table III). In 4 studies,[23,36–38] age (particularly >70 years) was strongly associated with stroke. In 2 studies,[23,38] anterior infarct,[23,38] poor Killip class,[23] and nonwhite race[38] were associated with ischemic stroke. Other treatment strategies, such as β-blocker use and angiography followed by percutaneous transluminal coronary angioplasty were not associated with cerebral ischemia.[38]

The question arises as to whether thrombolytic agents per se may cause ischemic stroke. Recent studies have documented the occurrence of stroke and other embolic complications after coronary thrombolysis, perhaps by lysing preexisting thrombi.[161–163] Based on the pharmacologic properties of the various agents, a causative role could be inferred if ischemic strokes occurred at a time consistent with their duration of action (<24 hours).[23] However, clinical studies in the prethrombolytic[1–5] and thrombolytic eras,[22–23,26–29,33] and echocardiographic studies of patients not treated with thrombolytic agents[7,8,10,13,16–19] indicate that most ischemic infarcts occur in the first few weeks and months after AMI.

Recent clinical studies evaluating the judicious use of streptokinase or urokinase to lyse left ventricular mural thrombi[164–166] or prosthetic valve thrombi[167,168] suggest that such therapy in the proper setting may be effective and relatively safe. Finally, although it is well known that ischemic stroke may be due to mechanisms other than cardiogenic embolism (vide supra), intensive evaluation of ischemic stroke in AMI patients is often not performed. Thus, it would seem that embolic stroke risk has not increased as a result of thrombolytic therapy.

One potentially valuable effect of thrombolytic therapy would be to lessen the occurrence of stroke by reducing the extent of myocardial damage and resultant left ventricular mural thrombus formation, which could lead to cerebral embolism. A number of studies suggest that although rt-PA may prevent left ventricular dilation after AMI,[169] neither streptokinase[11,170–173] nor rt-PA[172,174] consistently abolishes the incidence of left ventricular mural thrombus formation. A number of studies in patients not treated with thrombolytic agents indicate that anticoagulants[175–178] or aspirin[170] may reduce but not totally prevent[164,179–182] formation of left ventricular mural thrombi and embolization but may on occasion enhance left ventricular mural thrombus resolution.[12,14] Analysis of several large trials[1,3–5,183] suggests that long-term anticoagulant therapy may reduce the occurrence of stroke (Table I). It is possible that the combination of thrombolytic therapy and optimal level and duration of systemic anticoagulation may reduce left ventricular mural thrombus formation[111,184] and embolic complications. It has recently been shown that an aggressive regimen of rt-PA therapy (120 mg over 6 hours), early (within 4 hours of symptom onset) intravenous heparin, and aspirin followed by 3 months of warfarin therapy dramatically

reduced the occurrence of left ventricular mural thrombus formation in patients with anterior AMI to 9.2%, and no embolic events occurred.[185] In the future, well-designed studies with a large sample size could be performed to address this critical issue.

TABLE V Potential Risk Factors for Intracranial Hemorrhage After Thrombolytic Therapy

1. Age
2. Hypertension
3. Dosage of fibrinolytic agent or agents
4. Concomitant medications (calcium antagonists)
5. Prior neurologic disease
6. Cardiopulmonary resuscitation

POTENTIAL RISK FACTORS FOR INTRACEREBRAL HEMORRHAGE

The serious nature of intracerebral hemorrhage after thrombolytic therapy for AMI has led investigators to search for risk markers that would permit more careful patient selection. Potential risk markers for intracerebral hemorrhage are summarized in Table V.

Age: The mortality rate in elderly patients with AMI, even if treated with streptokinase[51] or rt-PA,[186] increases dramatically from <65 years to >75 years.[187] Since the elderly constitute an ever-increasing proportion of the population at risk and only 18% of eligible patients with AMI receive thrombolytic therapy, a number of investigators are seeking to extend treatment to this age group.[188–191] A recent meta-analysis[188] of 5 large trials[22,23,25–27,29] suggests that thrombolytic therapy may reduce mortality in the elderly when compared with control subjects (17.9% vs 22.1%, $p < 0.0001$). However, elderly patients may be more likely to have bleeding complications.[186,192] Some investigators have expressed the concern that elderly patients may have more defects in cerebrovascular integrity,[34,58] particularly since older age is associated with vascular disease that may be silent. In recent large coronary thrombolysis trials,[36,37] both streptokinase and rt-PA were associated with an excess of strokes in patients age >70 (>70 years: 2.7% rt-PA, 1.6% streptokinase; <70 years: 0.9% rt-PA, 0.8% streptokinase). In 2 studies[34,60] older age was not found to be a risk factor for intracerebral hemorrhage in patients treated with rt-PA, although the number of observations is small. In another study,[38] older patients had a significantly increased frequency ($p < 0.001$) of intracerebral hemorrhage when age was treated as a continuous variable. Some investigators recommend that a randomized placebo-controlled trial is necessary to determine safety and efficacy of thrombolytic therapy in patients who are >75 years old.[180] In the aggregate, although thrombolytic therapy for elderly patients may cause more strokes, the overall reduction in mortality with thrombolytic therapy suggests that the benefits may outweigh the risks.[191]

Hypertension: For many years, patients with blood pressure >180 systolic or >110 diastolic ("uncontrolled hypertension") were excluded from receiving thrombolytic therapy based on recommendations from the National Institutes of Health.[193] More recent work has examined the relation between a history of hypertension or acute hypertension and the occurrence of intracerebral hemorrhage after thrombolytic therapy. In ISIS-2,[26] although persistent severe hypertension was a relative contraindication, the mortality rate with systolic blood pressure >175 mm Hg was 5.7% in patients treated with streptokinase versus 8.7% in controls. In another trial, O'Connor and colleagues[34] found lower blood pressure in 4 patients with intracerebral hemorrhage than in 9 patients with ischemic stroke. Althouse and colleagues[60,194] reported that the occurrence of intracerebral hemorrhage in patients treated with rt-PA was associated with transient systolic blood pressure >180 mm Hg before treatment (2 of 9 [22%] with versus 1 of 147 [0.7%] without intracerebral hemorrhage). In TIMI-II,[38] intracerebral hemorrhage was more frequent among patients with histories of chronic hypertension than among patients without such a history (0.9% vs 0.4%), although this difference was not statistically significant. However, intracerebral hemorrhage occurred in 2 of 22 patients (9.1%) with systolic blood pressure >180 mm Hg or diastolic blood pressures >110 mm Hg before study entry compared with 9 of 647 patients (1.4%) without elevated blood pressure. One patient, who initially had severe hypertension but controlled blood pressure at the time of treatment, subsequently had recurring hypertension despite treatment and suffered an intracerebral hemorrhage. Gorelick and colleagues[195] reported a patient with poorly controlled hypertension who had a fatal cerebellar hemorrhage after intracoronary streptokinase. Although a significant incremental elevation in blood pressure may contribute to intracerebral hemorrhage occurrence in some cases, it is still possible that severe hypertension at the time of recognition of a change in neurologic function may reflect a systemic response to an acute cerebrovascular insult and not be the cause of stroke.

Dosage of fibrinolytic agents: The occurrence

of intracerebral hemorrhage in large thrombolytic therapy trials ranges from 0.18% for streptokinase[21–23,26,36,37] to 0.78% for rscu-PA,[40] although ascertainment bias (i.e., more frequent use of computed tomography scans or autopsies in more recent trials) or varied adjunctive therapeutic regimens may account for reported differences between agents. In TIMI-II,[38,63] 12 (1.3%) of 908 patients treated with 150 mg rt-PA and heparin and 11(0.4%) of 3,016 patients treated with 100 mg rt-PA and heparin developed intracerebral hemorrhage ($p < 0.01$). In other large trials using rt-PA 100 mg,[35–37] or streptokinase 1.5×10^6 units,[36,37] with[35–37] or without[36,37] heparin, intracerebral hemorrhage has been reported in 0.4–0.6% of patients. The apparent dose–response relation in the TIMI-II trial is confounded by the effect of more restrictive entry criteria in the 100-mg group, such as exclusion of patients with blood pressure > 180/110 mm Hg or history of acute cerebrovascular disease.[196,197] Patients who weigh less (especially women) have higher rt-PA concentrations during the infusion and, with more fibrinogenolysis, may have a greater risk of bleeding complications.[34,58] The effect of use of weight-adjusted thrombolytic regimens[64] on intracerebral hemorrhage occurrence remains to be determined.

Concomitant medications: It is possible that use of other medications may place patients at risk for intracranial bleeding. A number of drugs may affect platelet function, such as nonsteroidal anti-inflammatory agents, nitrates, and propanolol and contribute to bleeding.[198] Calcium antagonists have recently been shown to inhibit platelet aggregation[199] and arachidonic acid metabolism.[200] In TIMI-II,[38] use of calcium antagonists at study entry was associated with an increased frequency of intracerebral hemorrhage compared with patients not taking these drugs (8 of 538 [1.5%] vs 15 of 3,386 [0.045%], $p = 0.009$) and was not the result of any 1 agent's effect. Whether or not this association is due to chance, preexisting cerebrovascular disease, or an effect of calcium antagonists is unknown.[38]

Prior neurologic disease: In thrombolytic therapy trials, potential patients with histories of acute cerebrovascular disease within 2–3 months of entry have generally been excluded based on criteria of the National Institutes of Health.[193] In the TIMI-II pilot and early clinical trial,[38] patients with acute cerebrovascular disease in the 6 months before AMI presentation were excluded. In this phase of the study, 3 of 30 (10%) patients with a history of stroke, intermittent cerebral ischemic attack, or other neurologic disease had intracerebral hemorrhage compared with 8 of 639 (1.2%) without such histories ($p < 0.001$). At this point, the protocol was changed to make patients with histories of stroke or intermittent cerebral ischemic attacks ineligible. Since the observed excess risk of intracerebral hemorrhage in patients is based on observations in only 3 patients who had intracerebral hemorrhage in the high-risk group, the estimated increased risk is not precise (95% confidence interval about the odds ratio, 1.94–22.81).

Currently, a major international trial, Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO), has only 3 exclusion criteria, one of which is any history of neurologic disease. This decision was developed by a steering committee made up of members of the international cardiology and hematology communities.[65]

Cardiopulmonary resuscitation: It has recently been suggested that brief (< 10 minutes) cardiopulmonary resuscitation should not be a contraindication to thrombolytic therapy. Califf and colleagues[201] found no difference in transfusion requirements or in the incidence of pneumothorax and pneumopericardium in 62 patients receiving brief cardiopulmonary resuscitation when compared to 646 patients not requiring cardiopulmonary resuscitation. More prolonged cardiopulmonary resuscitation may lead to global hypoxic–ischemic encephalopathy, tissue disruption, and the risk of intracerebral hemorrhage.[189] At the present time, there has been no formal examination of this issue from the standpoint of intracranial bleeding.

POTENTIAL CAUSES OF INTRACRANIAL HEMORRHAGE

A number of variables may contribute to the occurrence of intracranial hemorrhage in specific individuals. These factors are summarized in Table VI.

Combined thrombolytic/anticoagulant/antiplatelet therapy: Basic aspects of fibrinolysis and mechanisms of action of the various thrombolytic agents have recently been reviewed.[193,202–204] Streptokinase and urokinase commonly induce a systemic fibrinolytic state. In some studies using rt-PA, a dose–response relation for induction of a systemic fibrinolytic state has been shown.[38,58,64,205,206] Several studies have shown a poor correlation between plasma rt-PA level and residual functional fibrinogen level,[207,208] as well as between the extent of the fibrinolytic state and bleeding complications.[50,58,198,209] One recent study has shown a strong correlation between rt-PA dose, plasma rt-PA,

TABLE VI Potential Causes of Intracranial Hemorrhage Following Thrombolytic Therapy

1. Acute hypertension
2. Combined fibrinolytic and antithrombotic treatment
3. Cerebrovascular pathology
   a. Arteriovenous malformation
   b. Cerebral amyloid angiopathy
   c. Berry aneurysm
   d. Microvascular lesions
4. Hemorrhagic transformation of cerebral infarction
5. Head trauma preceding therapy
6. After invasive cardiovascular procedures
7. Brain tumors

fibrinogen dosage[206] fibrinogen degradation product levels, and bleeding complications.[206] While the level of fibrinogen[58] and fibrin(ogen) degradation products[209] appear to correlate with the frequency of bleeding within treatment groups (streptokinase or rt-PA),[210] the occurrence of systemic bleeding is similar with all thrombolytic agents and relates more to the lysis of hemostatic plugs at sites of vascular invasion[198,204,209] and concomitant anticoagulation.[209]

The effect of thrombolytic therapy and the breakdown products of the fibrin clot on platelet function may also contribute to bleeding complications. Both streptokinase[210] and rt-PA[211] may prevent platelet aggregation, and rt-PA may promote dispersion of platelet aggregates.[212] Several other studies suggest that streptokinase[213–215] and rt-PA[216] may promote platelet aggregation. Discrepant results may be due to the fact that these in vitro observations reflect use of different SK preparations,[212] patient populations, and experimental conditions. The outcome of these effects in vivo are difficult to predict on the basis of in vitro studies and will depend on the nature of the insult, involved vascular bed, type and dose of agent, local conditions, and other factors.[217]

It is possible that adjunctive anticoagulant and antiplatelet therapies contribute to the occurrence of bleeding.[174,209] Increased bleeding may in part relate to use of intravenous[209] or subcutaneous[36,37] heparin. In ISIS-2,[26] there was a small excess (0.3%) of major bleeding requiring transfusion (major bleeding: 0.5% vs 0.2%, $p<0.001$). This excess was similar whether or not aspirin was used, but did depend upon planned use of intravenous heparin (0.7%), subcutaneous heparin (0.4%), or no heparin (0%). Preliminary data suggest that use of aspirin may enhance the effects of rt-PA on platelet disaggregation in vitro.[212] In 1 recent study,[218] prolongation of the bleeding time to >9 minutes (Ivy method) at 90 minutes after treatment initiation correlated with spontaneous bleeding, and bleeding was more frequent in patients taking aspirin. In 8 cases in the literature,[35,58,59,62,195] intracerebral hemorrhage occurred in association with documented severe hypofibrinogenemia. On occasion, marked elevation of fibrin(ogen) degradation products have also been observed.[58,59] In the majority of case reports, the activated partial thromboplastin time has been markedly prolonged.[35,50,58,59,62,195,219,220] In TIMI-II,[38] no important differences in fibrinogen, fibrin(ogen) degradation products, rt-PA antigen, or plasminogen levels were observed between patients with intracerebral hemorrhage, cerebral infarction, or between these groups and the other patients without cerebrovascular complications who had plasma specimens analyzed. In addition, the proportions of patients with or without an intracerebral hemorrhage or cerebral infarction who had at least 1 activated partial thromboplastin time >90 seconds were not different. Moreover, the occurrence of intracerebral hemorrhage is similar in patients who received 100 mg rt-PA and intravenous[35,38] or subcutaneous[36,37] heparin, the latter of which is not likely to be therapeutic in the first 24 hours of use.[221] Taken together, these data confirm the observations of others[31,49,58,198] that there is a poor correlation between the existence of a systemic lytic state and the occurrence of intracranial bleeding.

Recent work suggests that use of aspirin may be associated with an increased risk of hemorrhagic stroke.[222] This concern has prompted several investigators to hypothesize that aspirin use may contribute to the occurrence of intracranial bleeding after thrombolytic therapy[34] and to delay use of aspirin until 1 day after treatment.[38] Prolongation of the bleeding time by combined rt-PA and aspirin therapy appears to be maximal within the first 4 hours after initiation of rt-PA administration.[218] However, no intracerebral hemorrhages occurred in that small study and intracerebral hemorrhages often occur >4 hours after initiation of thrombolytic therapy.[36,38]

Cerebrovascular disease: It is possible that formation of blood clots in an arteriovenous malformation, either spontaneously or to limit the extent of prior occult bleeding episodes, may be inadvertently lysed by thrombolytic agents. Two cases of intracerebral hemorrhage due to arteriovenous malformations after thrombolytic treatment have been described in the literature.[38,223] In TIMI-II,[38] one patient who received 100 mg rt-PA developed intracerebral hemorrhage on day 2. Computed tomography scan showed an arteriovenous malformation adjacent to the hemorrhage. Pendlebury et

al[220] have recently reported a case of multiple intracerebral hemorrhages associated with cerebral amyloid angiopathy. The suspicion that other patients treated with thrombolytic agents may have amyloid as the cause of intracerebral hemorrhage is based on the predominant lobar location,[62,68] multiplicity,[35] and the increasing frequency in older patients.[38]

Only a handful of cases of subarachnoid hemorrhage occurring after thrombolysis for AMI have been documented in the literature.[48,50,51] Clinical details have been provided in only 1 case.[50] It is of interest that so few cases have been reported. This may reflect incomplete evaluation of stroke cases, lack of susceptibility of congenital berry aneurysms to rupture after thrombolytic therapy, or other reasons.

With regard to the several microvascular lesions that have been described in patients with spontaneous intracerebral hemorrhage (vide supra), it is tempting to speculate that thrombolytic therapy may unmask these lesions in susceptible patients and lead to intracerebral hemorrhage. For example, their location, multiplicity, fragility, and microscopic evidence of multifocal hemorrhage in autopsy studies[116–122] suggest that some cases with single or multiple intracerebral hemorrhages could be explained on this basis. However, in spontaneous intracerebral hemorrhage cases, it has been difficult to demonstrate the presence of these lesions in surgical specimens.[124,125] At the present time, no direct evidence exists to prove that these microvascular lesions could be unmasked by thrombolytic therapy to produce intracerebral hemorrhage. Further, these lesions are generally associated with chronic hypertension and the association of chronic hypertension with intracerebral hemorrhage in patients treated with thrombolytic agents is not strong.[38]

Head trauma preceding therapy: Subdural hematomas are a rare (0.01%) complication of thrombolytic therapy for AMI (Table III).[31,33,38] It is possible that use of thrombolytic agents may enhance fibrinolytic activity within an acute or preexisting subdural hematoma, promote bleeding, and produce symptoms. In 1 study,[38] a patient who developed a symptomatic subdural hematoma had a history of head injury 8 years before injury. In another patient, thrombolytic therapy may have enhanced formation of an acute subdural hematoma after a trivial head injury. In another study,[31] 1 patient developed a cerebellar intracerebral hemorrhage after unrecognized syncope and head trauma. Another patient developed a subdural hematoma. Although it is true that subdural hematomas may result from trivial head trauma preceding thrombolytic therapy, it is not known how often head injury precedes thrombolytic treatment in patients who did not develop the complication. It is also clear that head trauma may be associated with other forms of intracranial hemorrhage.

After invasive cardiovascular procedures: Both ischemic [25,224,225] and hemorrhagic[25,38,53,63,64] stroke have been reported to occur after coronary artery bypass graft surgery[25,38,53,64,224–226] and percutaneous transluminal coronary angioplasty.[63] Abnormal bleeding after cardiopulmonary bypass is well-known and is believed to be due to an acquired defect in formation of the platelet plug. Platelets are activated by passage through the oxygenation apparatus, causing secondary release and partial depletion of α granules. Severity of the defect relates to duration of cardiopulmonary bypass and use of platelet-active drugs. This defect is in general rapidly reversible[225,227] and can be prevented.[228] Hemostatic effects of rt-PA may contribute to systemic bleeding if cardiac surgery is performed soon after thrombolytic treatment.[228]

Intracranial hemorrhage after invasive cardiovascular procedures in conjunction with thrombolytic therapy has been reported to occur between <24 hours and 4 weeks after thrombolytic treatment.[25,38,53,63,64,224,226] Important parameters, such as clinical features, profile of illness, and presence or absence of anticoagulant therapy, have not been reported. In only one instance has the site of hemorrhage (posterior fossa) been specified.[53] In TIMI-II,[38] there was no increase in intracerebral hemorrhage occurrence in patients who received immediate or delayed coronary angiography and percutaneous transluminal coronary angioplasty. On the basis of published data,[25,53,63,64,224,226] it is not possible to distinguish between primary intracerebral hemorrhage and hemorrhagic infarction as the cause of symptoms in these cases. In addition, it is not possible to differentiate between the catheter procedure itself, the thrombolytic therapy, or the underlying cardiac or cerebrovascular disease as the cause of the stroke.

STROKE-RELATED MORTALITY AFTER THROMBOLYSIS

Limited data from only 4 large placebo-controlled trials[21,23,26–30] and 1 large comparative trial,[38] with varying study designs and degrees of neurodiagnostic precision, have provided sufficient information to evaluate the effect of thrombolytic therapy on stroke-related mortality (Table VII). Overall stroke-related mortality in these studies is 37%

(range 22–50%) in treated patients and 39% (range 18–75%) in untreated patients. In 3 studies,[23,26–28] there was no overall increase in risk of fatal stroke or permanent stroke-related disability due to streptokinase[23,26] or APSAC[27,28] therapy. Several studies have reported an early (<24 hours) excess mortality from intracerebral hemorrhage[23,26,29,30,38] whereas information from others[23,36,37] is limited[23] or not available.[36,37]

With regard to specific stroke subtypes, the overall mortality rate is as high as 38% for cerebral infarction and as high as 75% for intracerebral hemorrhage.[21–23,25–27,29,32,35,38,58,59,62,68] In TIMI-II,[38] the overall stroke-related mortality rate was 21 of 56 (38%). Ischemic cerebral infarction occurred in 29 of 3,924 (0.74%) patients, with a mortality rate of 6 of 29 (21%). In trials of anticoagulation therapy for cardiogenic embolism, patients who have hemorrhagic transformation of cerebral infarction often deteriorate and a 55% mortality rate has been reported.[114] In TIMI-II,[38] 1 of 8 (12.5%) patients who had hemorrhagic infarction died, perhaps suggesting a more favorable outcome from hemorrhagic infarction after thrombolytic therapy for AMI. Recent studies suggest that the in-hospital mortality rate for intracerebral hemorrhage has been reduced to between 44%[35] and 52%.[38] With 100 mg rt-PA, the mortality rate may be as low as 36%, and recovery with little or no residual deficit may occur in 54%.[38] Although fatal intracerebral hemorrhages have been reported,[24–26,29,41,42,47,54,57,58,60,219,220] some of the deaths may be unrelated to the intracerebral hemorrhage.[24,25,27–30,38,45,48,49,51] The reduction in mortality rate and more favorable outcome may reflect more careful patient selection, better control of the dosage of the fibrinolytic agent and concomitant therapies, timely diagnosis, and in some instances aggressive medical or surgical management, or both.[156] The occurrence of subdural hematoma appears to have a higher mortality rate (3 of 5, or 60%), but complete recovery is possible.[33,38]

In conclusion, stroke continues to be an important and one of the most dreaded complications of thrombolytic therapy for AMI. The assessment of stroke must include delineation of stroke subtype for optimal patient care and evaluation of the precise relation between thrombolytic therapy and stroke in this setting. The occurrence and mortality of ischemic cerebral infarction appears to be less in the thrombolytic era than in the prethrombolytic era, but the optimal adjunctive therapy has yet to be delineated. Intracranial hemorrhage associated with thrombolytic therapy for acute myocardial infarction in large series occurs in 0.3–0.6% of treated patients,[22,23,26,35–38] with an early mortality rate of 36–52%.[35,38] Available data suggest that the occurrence of and mortality from intracerebral hemorrhage might be further reduced by delineating the pathophysiology of these events, identifying patients at high risk, and optimizing adjunctive therapy. There appears to be a higher risk in elderly, significantly hypertensive, or demented patients, and possibly those with low body weight, recent head trauma, prior cerebrovascular disease, or use of calcium antagonists. Such patients are also likely to harbor a variety of microvascular lesions, which, when unmasked by thrombolytic therapy, may lead to intracranial hemorrhage.[111–122,211,215]

More research is needed to define the nature of cerebrovascular syndromes and the underlying disease in patients treated with thrombolytic therapy, in order to elucidate mechanisms and improve methods of prevention. Future studies are needed to delineate more accurately the risk of thrombolytic therapy for patients with various underlying conditions in order to optimize patient selection for therapy. In the meantime, great care should be exercised when considering therapy for such patients, particularly when multiple risk factors are present.

TABLE VII Overall Stroke-Related Mortality in Large Coronary Thrombolysis Trials

Study	No. of Patients* (%)	Treatment Group [n (%)]	Control Group [n (%)]
AIMS[27,28]	1,258	4/8	3/4
	(3)	(50)	(75)
ASSET[29,30]	5,011	11/51	6/34
	(13)	(22)	(18)
GISSI[23]	11,712	23/54	24/45
	(30)	(43)	(53)
ISIS-2[26]†	17,187	36/86	44/112
	(44)	(42)	(39)
TIMI-2[38]‡	3,924	21/56	—
	(10)	(38)	
Total	39,092	95/255	77/195
	(100)	(37)	(39)

*Plain numbers are numbers of patients, while numbers in parentheses are percentages of total patients where stroke-related mortality can be evaluated.
†Data include patients in streptokinase and streptokinase + aspirin groups. Hemorrhage includes "confirmed" and "possible" cases.
‡Data include intracerebral hemorrhage and subdural hematoma cases.

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Thrombin Antagonists and Antiplatelet Agents

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The clinical benefits of thrombolytic therapy for the treatment of myocardial infarction are recognized widely. However, 2 major limiting factors have become evident: (1) 20–25% of coronary arterial thrombi are resistant to lysis; and (2) coronary reocclusion occurs in 10–15% of patients. There is increasing evidence that both phenomena are caused by heightened procoagulant activity localized primarily at the site of atheromatous plaque rupture. Thrombin, the pivotal enzyme in all coagulation processes, is activated, stimulating fibrin formation and platelet aggregation. Platelet activation, by thrombin- and nonthrombin-mediated mechanisms, occurs as well, further increasing thrombotic tendency. Thus, a potent and well-localized procoagulant state may be continuously amplified, increasing both during and frequently after thrombolytic therapy. Current treatment strategies are designed to enhance fibrinolytic and anticoagulant activity, while neutralizing the expression of procoagulant factors. Thrombin antagonism and platelet inhibition, primarily with heparin and aspirin, respectively, form the mainstay of conjunctive therapy. Their benefits have been recognized, decreasing thromboembolic events and patient mortality. However, intrinsic limitations suggest that more potent and selective agents will be required to overcome effectively the problems of thrombolytic resistance and coronary reocclusion. In experimental models, specific thrombin antagonists and antiplatelet agents have shown superiority over heparin and aspirin. Further investigation to define the overall safety and efficacy profile of these newer agents will be required, however, prior to their widescale implementation in clinical practice.

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Under normal physiologic conditions, a delicate balance exists within the coronary vasculature between procoagulant and anticoagulant activity. The initiation and progression of coronary arterial thrombosis, however, reflects a pathologic imbalance in which procoagulant activity predominates, favoring platelet activation and fibrin deposition. Procoagulant activity may persist and at times may even increase, despite thrombolytic therapy. The development of treatment strategies for acute myocardial infarction (AMI) demands a clear understanding of the heightened procoagulant activity that typifies atherosclerotic coronary disease, thrombolytic resistance, and arterial reocclusion. Indeed, the administration of thrombin antagonists and antiplatelet agents in combination with thrombolytic therapy is designed to neutralize the persistent expression of procoagulation factors encountered in these settings.

A pharmacologic shift toward anticoagulation, however, may significantly impair physiologic hemostasis, thereby increasing hemorrhagic risk and limiting overall clinical benefit. This review explores the risk–benefit profile of thrombin antagonists and antiplatelet agents used conjunctively with thrombolytic therapy in the treatment of AMI.

CORONARY ARTERIAL THROMBOGENESIS

Coronary artery thrombi consist of both platelet- and erythrocyte-rich zones, with the former predominating in most instances. The platelet-rich zone exists primarily at the site of atherosclerotic plaque rupture, whereas erythrocyte-rich zones are found both proximal and distal to the area of vascular injury.

Platelets play a primary role in coronary arterial thrombogenesis; three distinct mechanisms are involved, including: (1) adhesion to subendothelial surfaces and pathologic substrate following plaque rupture; (2) aggregation to adjacent platelets; and (3) activation of the coagulation cascade with fibrin deposition at the site of vascular injury (Figure 1).

Platelet adhesion is mediated by numerous surface receptors with high affinity for adhesive glycoproteins found within the vascular subendo-

thelium (e.g., collagen types I and III, fibronectin, vitronectin). Glycoprotein (GP) Ib is the most well known; however, other receptors, including GPIa/IIa, GPIc/IIa, and GPIV, play important roles in platelet adhesion as well. Platelet aggregation is mediated primarily by GPIIb/IIIa. When activated, GPIIb/IIIa can bind several proteins, including von Willebrand factor, fibronectin, and thrombospondin, although fibrinogen is the predominant protein that is bound. Fibrinogen's dimeric structure allows interaction with 2 platelets simultaneously, fostering aggregation. Following a series of platelet–coagulation protein interactions, thrombus growth occurs.

In addition to inciting platelet adhesion and activation, atheromatous plaque rupture exposes tissue factor, the lipoprotein procoagulant in tissue thromboplastin, which is present in both the arterial subendothelium and the plaque itself.[1,2] Tissue factor initiates activation of the extrinsic coagulation pathway by serving as a cofactor to Factor VIIa, leading to Factor X activation. Because Factor VIIa is also capable of activating Factor IX, the intrinsic coagulation pathway can be activated as well. In either case, the common end product is thrombin.

Derived from the C-terminal portion of prothrombin, thrombin contains 2 polypeptide chains, A and B, of 49 and 259 amino acid residues, respectively. The catalytic center resides on the B chain and is responsible for a number of diverse enzymatic activities, including: (1) potentiation of the tenase and prothrombinase complexes via interaction with Factors V, VIII, and X; (2) conversion of fibrinogen to fibrin monomer; (3) exposure of fibrin monomer polymerization sites; and (4) Factor XIIIa-mediated fibrin polymer stabilization (Figure 2).[3] In addition, thrombin is a potent stimulus for platelet aggregation and release, essential for thrombus growth.[4] The binding of thrombin to platelets is a complex equilibrium process that involves high- and low-affinity receptor sites with dissociation constants of 5.9×10^{-7} M and 1.4×10^{-9} M, respectively.[5,6]

THROMBIN ACTIVITY IN ACUTE MYOCARDIAL INFARCTION

Thrombin activity is increased in patients experiencing AMI.[7] Of clinical importance, continued thrombin activation at the site of original plaque rupture and within areas of residual mural thrombosis influence directly both thrombolytic efficacy and arterial reocclusion. Indeed, heightened thrombin activity, as indirectly assessed by fibrinopeptide A or thrombin–antithrombin complexes in plasma, identifies patients at risk for either unsuccessful reperfusion or initial recanalization followed by early reocclusion.[8,9]

The intravenous administration of a fibrinolytic agent results in a conversion of plasminogen to

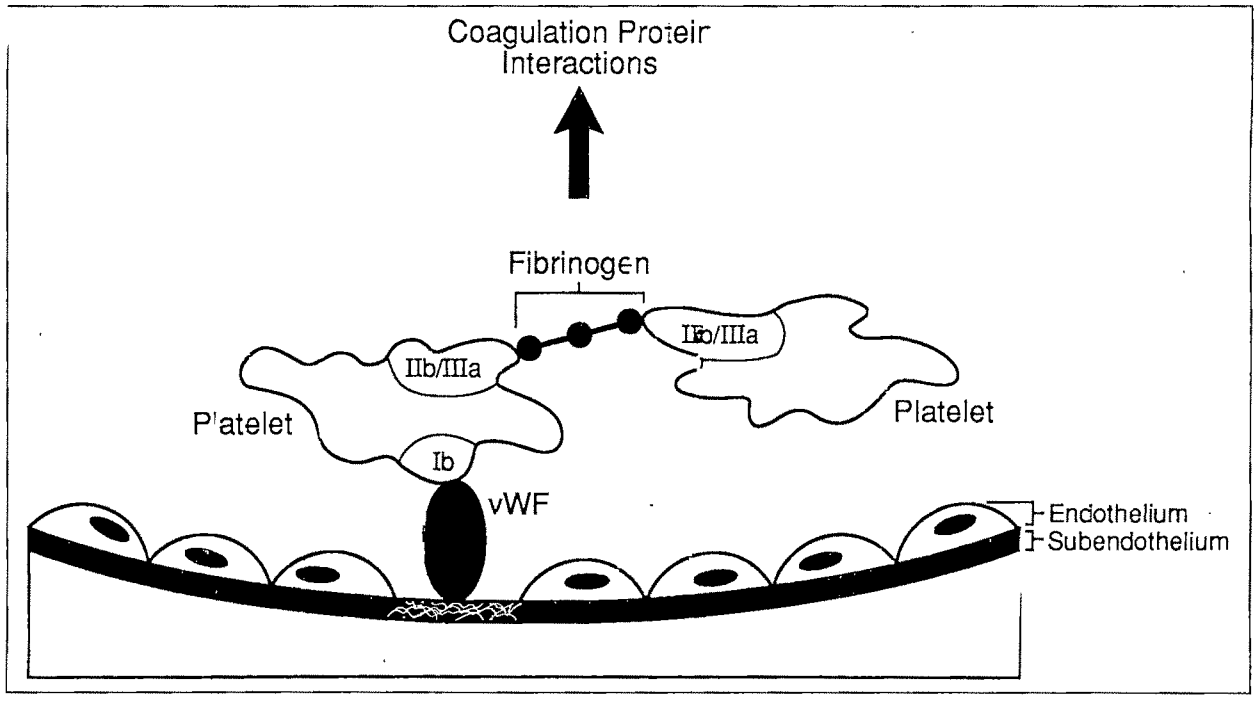


FIGURE 1. Schematic representation of a localized area of vascular injury. Platelet adhesion and aggregation occur by specific receptor-mediated mechanisms. Following a series of platelet–coagulation protein interactions, a platelet-fibrin thrombus forms.

plasmin. Similar to other serine proteases, plasmin is capable of Factor XII activation (contact activation), which in turn activates prekallikrein, Factor XI, and high molecular weight kininogen. Plasmin-mediated contact activation may also activate Factor XIII.[10] Therefore, it appears that plasmin generation is capable of enhancing both fibrinolytic and procoagulant activity. In further support of the latter, both streptokinase[11] and recombinant tissue plasminogen activator (rt-PA)[12] have been shown to increase plasma fibrinopeptide A concentrations shortly after intravenous administration. Although this observation may reflect a plasmin-mediated release or exposure of thrombin molecules on the thrombus surface,[13] a series of in vitro studies performed by Weitz et al[14] suggest that rt-PA, and possibly other plasminogen activators as well, can cleave thrombin-susceptible arginine–glycine bonds on the α- and β-chains of fibrinogen. The "thrombin-like" activity of rt-PA is supported by studies showing a direct correlation between treatment initiation, increasing fibrinopeptide A concentrations, and coronary arterial reocclusion.[15]

PLATELET ACTIVITY IN ACUTE MYOCARDIAL INFARCTION

Patients with angiographically documented atherosclerotic coronary artery disease exhibit increased platelet activity.[16] In the setting of AMI the coronary vascular bed is a major site of platelet activation. Aggregating platelets are involved directly in thrombus formation and moreover can trigger intense focal vasoconstriction following activation and release of 2 potent vasoactive mediators—thromboxane A_2 and serotonin.[17] In addition, an increased density of platelet thromboxane A_2/prostaglandin H_2 receptors has been documented recently in patients with AMI.[18]

Under ideal conditions, coronary reperfusion following rt-PA administration is achieved 75–80% of the time. Therefore, 20–25% of all coronary arterial thrombi are resistant to lysis. Although nonthrombogenic mechanisms, including vasospasm, luminal compression by intraplaque hemorrhage, and arterial dissection, may contribute, intrinsic resistance of the thrombus itself to lysis must also be considered.

Preformed whole blood or plasma clots are lysed readily with rt-PA in low concentrations, whereas platelet aggregates formed in platelet-rich plasma require a much higher concentration for disaggregation.[19] Similar findings have been observed in vivo: erythrocyte-rich thrombi are consistently lysed following an intravenous infusion of rt-PA in low doses, in contrast to platelet-rich thrombi, which are relatively resistant.[20] Although the underlying mechanisms are still under investigation, comparative analysis of the rates of platelet-bound fibrinogen proteolysis versus ambient plasma fibrinogenolysis suggests that rt-PA can facilitate platelet disaggregation through a kinetically selective breakdown of cohesive fibrinogen[19] and may also affect intracellular signaling, attenuating calcium flux and serotonin release.[21] Higher rt-PA concentrations may be required for lysis, however, due to the release of platelet-associated growth factors (including epidermal growth factor and transforming growth factor b) and platelet lysates, which augment plasminogen activator inhibitor, attenuating local fibrinolytic activity.[22]

The effects of rt-PA on platelet surface receptor glycoproteins, specifically GPIb, have been examined previously in patients participating in the

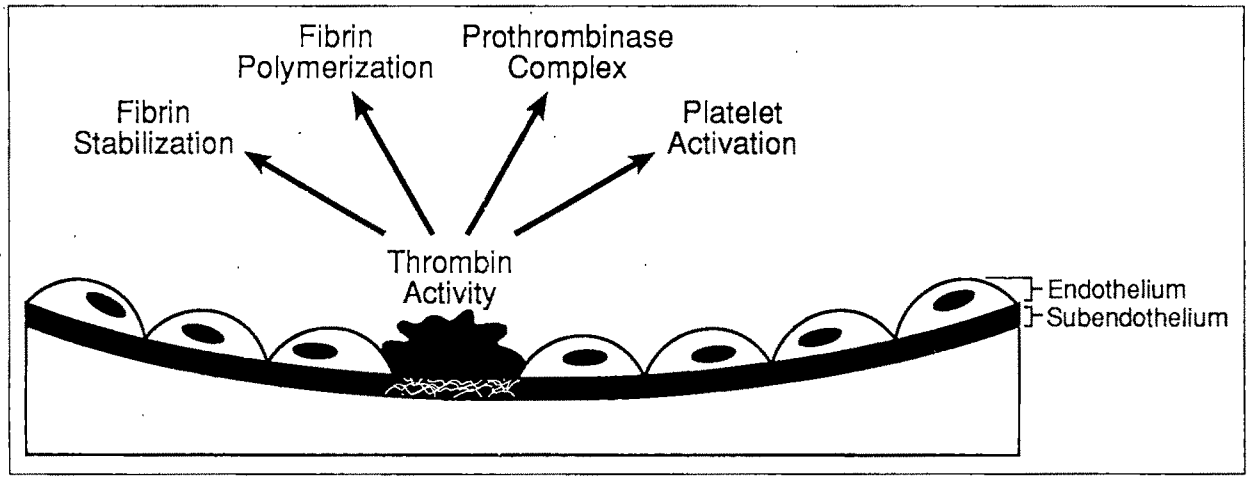


FIGURE 2. Thrombin activation occurring at a site of plaque rupture and mural thrombosis is responsible for a marked increase in local procoagulant activity, contributing to thrombolytic resistance and coronary reocclusion. VWF = von Willebrand factor.

Second Thrombolysis in Myocardial Infarction (TIMI-II) trial.[23] Following an intravenous infusion of rt-PA, an increase in plasma glycocalicin, a proteolytic fragment derived from GPIb, was noted. In addition, a concomitant decrease in whole platelet GPIb and a slight increase in platelet surface GPIb were observed, suggesting that platelets can replenish surface GPIb over time by recruitment from an intraplatelet storage pool. In concentrations achieved commonly after a standard rt-PA bolus[24] or a maintenance infusion,[25] platelet aggregation in response to a variety of stimuli, including ristocetin, adenosine diphosphate, thrombin, and collagen, is attenuated, raising the possibility that GPIa/IIa and GPIIb/IIIa may also be altered.[26]

In contrast, several investigators have observed platelet activation following thrombolytic therapy.[27,28] Although this finding may reflect heightened thrombin activation,[23] differing effects of plasmin generation must be considered as well. In low concentrations (<0.5 CU/ml), plasmin adversely affects platelet surface glycoprotein structure and function[29–31] and has been shown to inhibit arachidonic acid mobilization.[32] In high concentrations (>1.0 CU/ml), however, plasmin is capable of increasing platelet aggregation. A number of explanations have been proposed, including: (1) plasmin-treated platelets have an increased number of available fibrinogen binding sites on their surface[33]; (2) platelet suspensions incubated with plasmin undergo activation and release[34]; and (3) plasmin mediates a time- and dose-dependent phosphorylation of platelet proteins, causing a rise in cytosolic calcium and activation of both phospholipase and protein kinase C.[35]

THROMBIN ANTAGONISTS

Clinical benefits: Heparin is a heterogeneous mucopolysaccharide that accelerates an inhibitory interaction between antithrombin III and a number of circulating anticoagulant proteins, including thrombin (Factor II) and Factor X. Following intravenous administration, approximately 33% of the circulating heparin molecules bind to antithrombin III. The remaining 67% have minimal anticoagulant activity at therapeutic concentrations. At high concentrations, however, an antithrombin effect can occur via heparin's interaction with a second plasma protein, heparin cofactor II.[36–38]

Heparin has been shown to reduce fibrinopeptide A concentrations in patients with AMI.[39] Because plasma fibrinopeptide A reflects ongoing thrombin activation, an inhibitory effect of thrombin would thus suggest a reduction in fibrin monomer synthesis and, ultimately, thrombus growth. This may explain, at least in part, heparin's observed enhancement of t-PA–mediated thrombolysis in a number of experimental thrombosis models.[40–43] Additional hypotheses include: (1) increased amidolytic plasmin activity[44,45]; (2) enhanced t-PA–plasminogen interactions[45]; (3) stimulation of endothelial cell t-PA release[46]; and (4) enhanced t-PA binding to fibrin.[47]

Despite in vitro and experimental support, however, a recent clinical study failed to identify a meaningful facilitative interaction between heparin and rt-PA[48]; 90-minute patency, vessel diameter, and the success rate for rescue coronary angioplasty were essentially the same whether or not intravenous heparin was administered prior to rt-PA.

Following deep arterial injury, heparin has been shown to decrease platelet deposition and thrombus formation.[49] Indeed, 3 recently completed clinical trials[50,51] have confirmed the benefits of intravenous heparin after thrombolytic therapy with rt-PA, reducing reocclusion primarily within the initial 24–48 hours. Of additional clinical relevance, systemic states of therapeutic anticoagulation (indicated by an activated partial thromboplastin time of 1.5–2.0 times the control) were associated with sustained arterial patency. These findings are consistent with those of previous clinical trials that included patients with thromboembolic disease, showing that the overall efficacy of heparin is optimized if a systemic state of anticoagulation is achieved and maintained.[52–55]

The overall clinical impact of heparin's ability, particularly in patients receiving rt-PA, to reduce early coronary reocclusion should translate into a reduction in both recurrent infarction and mortality. Indeed, a meta-analysis of previous trials indicates that heparin reduces recurrent infarction and early mortality by 22% and 16%, respectively.[56] Despite the known limitations of subcutaneous heparin,[57] the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2)/International Study,[58,59] Third International Study on Infarct Survival (ISIS-3) (unpublished data), and the combined experience (unpublished data) suggest that heparin administered conjunctively with thrombolytic therapy is associated with significant reductions in both reinfarction and early vascular death. Interestingly, in these trials the greatest benefit was observed in patients receiving streptokinase.[58,60] In GISSI-2, for example, patients randomized to streptokinase and subcutaneous

heparin experienced a 7.9% mortality rate, compared with 9.2% among patients treated with streptokinase alone ($p < 0.02$). In contrast, patients randomized to rt-PA had similar mortality rates with or without subcutaneous heparin.

The observed difference in clinical response to heparin may be explained by the greater systemic anticoagulant effect produced by streptokinase, which, coupled with the modest effect of subcutaneous heparin, resulted in an adequate antithrombotic state. However, rt-PA rarely produces a significant systemic anticoagulant effect, and, therefore, the low doses of subcutaneous heparin used in GISSI-2 (and ISIS-3) would probably be inadequate to prevent coronary reocclusion.

The potential added benefit of full-dose intravenous heparin is currently being investigated in the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) trial.

Despite its recognized benefits, however, heparin may not represent the optimal conjunctive agent because of its inability to inhibit consistently and effectively thrombin- and platelet-mediated arterial thrombosis. These important limitations may be explained by: (1) the release of heparin-neutralizing proteins (platelet Factor 4, thrombospondin) from activated platelets; (2) inaccessibility of heparin to clot-bound thrombin, platelet-bound Factor X, and thrombin located in the subendothelial matrix; (3) platelet activation of meizothrombin, which is resistant to heparin neutralization; (4) heparin-induced platelet activation; and (5) fibrin II monomer-mediated heparin neutralization.[61–69]

Hirudin is a selective and specific thrombin inhibitor derived from the peripharyngeal glands of medicinal leeches (*Hirudo medicinalis*). A single polypeptide chain composed of 65 amino acids, hirudin inactivates thrombin by forming a nearly irreversible 1:1 stoichiometric complex, neutralizing intrinsic and extrinsic coagulation and inhibiting thrombin-mediated platelet activation.[70–73] It has been shown to be an effective antithrombotic agent in various experimental models[74–76] and, unlike heparin, effectively neutralizes clot-bound thrombin.[66,77] In a model of deep arterial injury, recombinant hirudin (r-hirudin) prevented mural thrombus formation more effectively than heparin.[78,79] Evidence suggesting that r-hirudin may improve thrombolytic efficacy while preventing reocclusion has also been obtained.[80] At the present time, Phase 2 clinical trials (Thrombolysis in Myocardial Infarction [TIMI]-V and -VI) are in progress, designed to evaluate the safety and efficacy of r-hirudin when administered conjunctively with thrombolytic therapy.

A competitive thrombin inhibitor, argatroban, has shown considerable promise in experimental models of platelet-rich arterial thrombosis, preventing reocclusion more effectively than heparin[81] and enhancing reperfusion when given in combination with rt-PA.[82] Its role in patient care, however, has not been defined.

Additional antithrombin III-independent inhibitors of thrombin activity including hirugen, hirulog, and D-Phe-Pro-Arg-chloromethyl ketone (PPACK) have each shown promise in experimental thrombosis models; however, clinical experience is lacking at this time.[83–86]

Clinical risks: The most common adverse effect of heparin administration is hemorrhage. Other complications include thrombocytopenia (with or without thrombosis), alopecia, skin necrosis, hypoaldosteronism, osteoporosis, and hypersensitivity reactions.

The anticoagulant response to heparin varies widely among patients with thromboembolic disease, which is a reflection of its commercial heterogeneity and complex pharmacokinetics. Compounding this problem further is the extreme variability in sensitivity of the reagents used in activated partial thromboplastin time measurements to heparin.[87] The difference in responsiveness between thromboplastins makes comparisons of anticoagulant response among laboratories difficult.

In addition to its anticoagulant properties, heparin inhibits platelet function, primarily by impairing serotonin release,[88,89] and increases vascular permeability[90]; both effects add to its overall hemorrhagic potential. Moreover, heparin, unlike other sulfated glycosaminoglycans, exhibits important antihemostatic effects that are independent of its anticoagulant effects. Indeed, in vitro experiments have shown that heparin competitively inhibits the hydrolysis of adenosine triphosphate by myosin adenosine triphosphatase.[91] This suggests that heparin binds to a myosin-like molecule of smooth muscle cells, inhibiting vascular contractility and thus impairing an important component of primary hemostasis.[92]

There is indirect evidence that the frequency of bleeding increases with the dose of heparin, particularly with intermittent intravenous administration. Other factors predisposing patients to heparin-related hemorrhage include advanced age, renal insufficiency, serious concurrent illness, and chronic ethanol abuse.[93–95]

In patients receiving thrombolytic therapy, ob-

TABLE I Hemorrhagic Complications in Major Thrombolytic Therapy Trials

Trial	Patients (n)	Thrombolytic Agent	Total Dose	Hemorrhagic Events (%) Major	Minor
TIMI-I*	143	rt-PA	80 mg†	15.4	17.5
TIMI-I*	147	SK	1.5 MU	15.6	15.6
ECSG*	721	rt-PA	100 mg	27.3	27.3
AIMS	1,004	APSAC	30 U	5.0	5.0
GISSI-1	11,806	SK	1.5 MU	0.3	3.7
ASSET	5,011	rt-PA	100 mg	1.3	6.3
ISIS-2	17,187	SK	1.5 MU	0.5	3.5
		SK/	1.5 MU/	0.5	7.8
		ASA	162.5 mg		
GISSI-2	12,490	SK	1.5 MU	0.7	6.9
		SK + heparin		1.2	—
		rt-PA	100 mg	0.5	8.0
		rt-PA + heparin		0.6	—
International Study	20,891	SK	1.5 MU	0.6	—
		rt-PA	100 mg	0.5	—
ISIS-3	46,092	SK	1.5 MU	0.9	—
		rt-PA‡	0.6 MU/kg	0.9	—
		APSAC	30 U	1.0	—

*Invasive protocol.
†Predominantly double-chain (G11021; no longer available).
‡(Duteplase; Burroughs-Wellcome).
AIMS = APSAC Intervention Mortality Study; APSAC = anisoylated plasminogen-streptokinase activator complex; ASA = aspirin; ASSET = Anglo-Scandinavian Study of Early Thrombolysis; ECSG = European Cooperative Study Group; GISSI-1 = Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico; GISSI-2 = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; ISIS-2 [3] = Second [Third] International Study on Infarct Survival; rt-PA = recombinant tissue plasminogen activator; SK = streptokinase; TIMI = Thrombolysis in Myocardial Infarction, Studies I and II.

served rates of hemorrhage have varied widely, reflecting differences in data collection, methodology, reporting, and defined end points. Overall, however, patient selection and study protocols (invasive vs noninvasive) have clearly had an important impact on the incidence of hemorrhagic events (Table I).

A majority of clinical trials performed to date have included intravenous or subcutaneous heparin. Using strict criteria and a comprehensive data-gathering protocol, the TIMI-II investigators[96] observed a 3.0% major hemorrhagic event rate among patients treated conservatively in whom cardiac catheterization or surgery was not performed. In this group, major or minor hemorrhagic events occurred in 11.3%. In contrast, patients undergoing angiography experienced a 7.7% incidence of major hemorrhagic events. Among patients receiving 100 mg rt-PA in combination with intravenous heparin and oral aspirin, the rate of confirmed intracranial hemorrhage was 0.5%. Of considerable importance for patient care, patients having activated partial thromboplastin times >90 seconds during the first 5 days of treatment were found to have a 2-fold increased risk of major or minor hemorrhagic events. Further, a platelet count decreasing to $\leq 100 \times 10^9$/liter within 3 days of study entry was associated with a 7-fold increased risk of hemorrhagic events. The temporal relation between thrombocytopenia and the heparin infusion suggested that heparin may have contributed directly

Thrombocytopenia is a well-recognized complication of heparin therapy.[97,98] It is more common with heparin derived from bovine lung than porcine intestinal mucosa, with incidence rates of 16% and 6%, respectively. The most feared and devastating complication of heparin-induced thrombocytopenia (aside from life-threatening hemorrhage) is arterial thrombosis, occurring in approximately 0.5% of patients.[98]

r-Hirudin is a unique thrombin inhibitor that prevents not only fibrinogen clotting, but also other thrombin-catalyzed reactions, such as activation of Factors V, VIII, and XIII as well. Because of its high affinity for thrombin, in vitro coagulation tests, including the thrombin time, activated partial thromboplastin time, and prothrombin time, vary with different hirudin concentrations. The most sensitive assay is the thrombin time, which is prolonged even with extremely small amounts of hirudin. In contrast, the prothrombin time offers poor sensitivity. Therefore, the anticoagulant activity of r-hirudin is often determined by measuring the activated partial thromboplastin time.[99–103] In contrast to heparin, the hirudin–activated partial thromboplastin time dose–response relation is shallow and linear, allowing a more controlled and predictable regulation of systemic anticoagulation. In addition, previous experimental studies have shown that r-hirudin administered in doses sufficient to prolong the activated partial thromboplastin time to 1.5–2.0 times the control have profound antithrombotic potential, whereas heparin given in doses eliciting a similar anticoagulant response rarely prevent thrombosis.[79–80]

r-Hirudin effectively inhibits thrombin-induced platelet activation and release.[104] However, it does not influence platelet reactions induced by other activators, such as epinephrine, adenosine diphosphate, collagen, or serotonin. As a result, r-hirudin typically does not prolong the bleeding time, unless it is given in large doses (beyond that required for an antithrombotic effect).[105] In animal models, blood loss from standardized ear incisions was minimal at doses shown to be antithrombotic in the same animal species. Only in doses 20-fold above those required for antithrombotic action was slight bleeding observed.[106] This property, coupled with favorable antithrombotic and anticoagulant profiles, suggests that hemorrhagic complications associated with r-hirudin administration may be less

TABLE II Thrombolytic Therapy Trials Including Aspirin

Trial	Patients (n)	Aspirin (dose)	Thrombolytic Agent	Mortality
ISIS-2	4,300	—	—	13.2% (5-week)
	8,587	162.5 mg/day	—	9.4%
	8,592	—	SK (1.5 MU)	9.2%
	4,292	162.5 mg/day	SK (1.5 MU)	8.0%
TIMI-II*	1,626	80–324 mg/day	rt-PA (100 mg)	4.7% (6-week)
ECSG	355	250 mg IV	rt-PA (100 mg)	2.8% (2-week)
		75–125 mg qod		5.2% (12-week)
GISSI-2	5,202	300–325 mg/day	rt-PA (100 mg)	8.7% (in-hospital)
ISG	5,205	300–324 mg/day	SK (1.5 MU)	9.2% (in-hospital)
ISIS-3	13,295	162 mg/day	SK (1.5 MU)	10.5% (5-week)
	13,328	162 mg/day	APSAC (30 U)	10.6%
	13,290	162 mg/day	rt-PA (0.6 MU/kg)†	10.3%

*Conservative treatment group.
†Duteplase.
ISG = International Study Group; IV = intravenous; qod = every other day. See Table I for other abbreviations.

than with heparin. Providing further support, the combination of rt-PA and r-hirudin has been shown in an experimental model to cause less bleeding than rt-PA and heparin.[107]

As mentioned previously, the safety profile of r-hirudin administered conjunctively with thrombolytic therapy will be explored in TIMI-V and TIMI-VI.

Although r-hirudin may reduce hemorrhagic potential, under certain clinical conditions physiologic hemostasis may be significantly impaired. In contrast to heparin, r-hirudin is not neutralized by protamine sulfate. A major question that must be addressed prior to its widescale clinical use, therefore, is, "How can the anticoagulant effect of r-hirudin be neutralized?"

At the present time, an antagonist for r-hirudin is not available. The lines of ongoing investigation include monoclonal antibodies, selectively increasing thrombin generation with activated prothrombin complex concentrates, desmopressin, and fresh frozen plasma, as well as physical methods of removal, such as immunosorption, plasmapheresis, and hemoperfusion.[108]

Although hirudin is a foreign protein, both the native and recombinant forms are weak immunogens. Therefore, it is anticipated that major allergic responses will rarely be observed.[109,110]

ANTIPLATELET AGENTS IN ACUTE MYOCARDIAL INFARCTION

Clinical benefits: Aspirin, an irreversible acetylator of platelet cyclooxygenase, administered in the early hours following AMI onset can prevent the anticipated increase in thromboxane A_2 generation,[111] an effect maintained with continued administration. Pretreatment with aspirin may also abolish an rt-PA associated increase in thromboxane A_2.[112] In addition, cyclic flow variations, a harbinger of coronary reocclusion in experimental models caused by platelet thrombi forming in sites of endothelial injury, can be inhibited by aspirin.[113]

Patients with a history of AMI are at risk for recurrent infarction and other thromboembolic events. In their comprehensive review of clinical trials, the Antiplatelet Trialists Collaboration group[114] identified a marked benefit from aspirin, decreasing significantly recurrent infarction, stroke, and vascular mortality by 31%, 42%, and 13% respectively.

In the AMI setting, aspirin administration has been shown to reduce vascular mortality by 23%, a benefit maintained at 2-year follow-up.[115] An added survival benefit was observed with a regimen consisting of intravenous streptokinase and oral aspirin. Moreover, aspirin reduced both the overall stroke rate and the incidence of recurrent infarction as well. A strikingly low mortality rate (2.8% at 14 days) was observed in the European Cooperative trial of rt-PA, which included early intravenous aspirin (250 mg) followed by oral aspirin (75–125 mg) every other day.[116] Patients enrolled in the TIMI-II trial[117] also received aspirin daily (80–325 mg), and experienced low 42-day mortality and reinfarction rates, 4.7% and 5.4%, respectively. In contrast, aspirin was not included in the Anglo-Scandinavian Study of Early Thrombolysis (ASSET) protocol,[118] and although an improvement in survival with rt-PA was observed, the 4-week mortality rate of 7.2% was higher than that observed in either the European Cooperative Study Group (ECSG) trial or the TIMI-II trial despite an identical dose of rt-PA (100 mg) (Table II).

The beneficial effects of aspirin in patients receiving thrombolytic therapy most likely translate into its ability to prevent coronary reocclusion.[119] In currently recommended doses (160–325 mg/day), aspirin does not appear to improve throm-

TABLE III Antiplatelet Agents in Thrombolytic Therapy

Agent	Mechanism of Action
Aspirin	Inhibit platelet cyclooxygenase
LY53857	Serotonin-receptor antagonist
SQ29548	Thromboxane A_2-receptor antagonist
Sulotroban	Endoperoxide/thromboxane A_2-receptor antagonist
AH23848/L636,499	Endoperoxide/thromboxane A_2-receptor antagonist
Pirmagrel	Thromboxane synthase inhibition
GR32193	Thromboxane A_2-receptor antagonist
Iloprost	Prostacyclin analogue
Ciprostene	Prostacyclin analogue
Prostaglandin E_1	Inhibit platelet aggregation
LJ-CP3	Inhibit GPIIb/IIIa receptor
10E5	Inhibit GPIIb/IIIa receptor
7E3	Inhibit GPIIb/IIIa receptor
RGDY	Inhibit GPIIb/IIIa receptor
Aurintricarboxylic acid	Inhibit GPIb–von Willebrand interaction

bolytic efficacy[120] (possibly because of high circulating catecholamine concentrations following AMI that attenuate aspirin's platelet-inhibiting properties).[121,122] Further, aspirin has not been shown to reduce either infarct size[123] or ventricular irritability to a significant degree.[124]

The high incidence of thrombolytic resistance and coronary reocclusion in clinical practice has prompted intense investigation of a broad range of antiplatelet agents (Table III). Cyclic flow variations can be abolished with either the serotonin-receptor antagonist LY538537 or the thromboxane A_2-receptor antagonist SQ29548[124]; combined administration of these agents may have additive properties in the prevention of reocclusion.[125–127] In an animal thrombosis model, the endoperoxide/thromboxane A_2 receptor antagonist Sulotroban (BM 13.177) has been shown to both reduce the time required for rt-PA–mediated thrombolysis, and prevent reocclusion as well.[128] Similar findings were observed with another endoperoxide/thromboxane A_2 inhibitor, AH23848/L636,499.[129] Pirmagrel, a thromboxane synthetase inhibitor, has also been shown to enhance thrombolytic efficacy with rt-PA,[130] as has the irreversible thromboxane A_2-receptor antagonist (GR32191).[131] Although encouraging results were reported initially with the stable prostacyclin analogue iloprost,[132] a recent clinical study failed to reveal a beneficial effect when it was combined with rt-PA.[133] Further, a high incidence of adverse effects including systemic hypotension and reflex tachycardia was observed. The ability of iloprost to increase hepatic blood flow, which may increase rt-PA degradation and reduce steady-state plasma t-PA antigen concentrations, may explain the disappointing results.[134] Clinical studies with another prostacyclin analogue, ciprostene, may be warranted, however, given its ability to enhance thrombolysis without altering rt-PA kinetics.[135] Prostaglandin E_1, in doses that did not alter systemic blood pressure, accelerated the rate and augmented the extent of clot lysis produced by rt-PA in a rabbit jugular vein thrombosis model.[136] Of additional interest, prostaglandin E_1 attenuated the transient hyperaggregable response of platelets to adenosine diphosphate following the rt-PA infusion.[136]

Monoclonal antibodies, which block the platelet GPIIb/IIIa receptor, have been developed. The F(ab')2 fragment of these antibodies can block ex vivo platelet aggregation in response to even high doses of agonists or combinations of agonists. In a nonhuman primate (monkey) carotid artery thrombosis model, monoclonal GPIIb/IIIa antibodies (7E3 and 10E5) prevented thrombus formation in doses that did not always inhibit platelet aggregation or prolong the bleeding time.[137] In a canine coronary thrombosis superimposed on a high-grade stenosis model, combined administration of rt-PA and [7E3–F(ab')2] reduced the time to reperfusion and also prevented reocclusion. In a similar experimental model [7E3–F(ab')2, 0.8 mg/kg] prevented rethrombosis following rt-PA–induced thrombolysis; however, the restoration of coronary blood flow was not maintained, thereby suggesting the possibility of nonplatelet or thrombus-mediated alterations in coronary vasomotor tone as a cause of reduced blood flow.[138] In an ex vivo system, the specific GPIIb/IIIa monoclonal antibody LJ-CP3 inhibited platelet deposition on severely damaged vessel walls under high local shear rates.[139]

Competitive inhibitors of the GPIIb/IIIa receptor such as arginine–glycine–aspartate–*O*–methyltyrosine amide (RGDY), which compete with fibrinogen for the GPIIb/IIIa receptor, have also been shown to prevent coronary arterial reocclusion.[140] The pivotal role of von Willebrand factor in shear-induced platelet aggregation suggests that von Willebrand factor–GPIb-mediated platelet activation may be important in acute coronary occlusion following thrombolysis. Indeed, the ability of aurintricarboxylic acid (an inhibitor of von Willebrand factor–GPIb interactions) to prevent cyclic flow variations in a canine model of coronary arterial thrombosis indicates that further investigation is warranted.[141,142]

Clinical risks: Antiplatelet strategies may be associated with an increased risk of hemorrhagic complications. Combined administration of aspirin and rt-PA has been shown to prolong template bleeding times and increase spontaneous bleed-

ing.[143] In ISIS-2,[115] however, aspirin use was associated with an increased incidence of minor bleeding events. It did not influence the risk of major events, even when combined with streptokinase.

The primary prevention trials of AMI[144,145] have suggested that aspirin administration may be associated with an increased incidence of intracerebral hemorrhage. In TIMI-II,[146] a dose of 150 mg rt-PA combined with aspirin and heparin was associated with an excess of neurologic events. A protocol change, which omitted aspirin during the first 24 hours of treatment and decreased the rt-PA dose to 100 mg, reduced the incidence of intracranial hemorrhage significantly. Although it is possible that the omission of early aspirin administration was responsible for the decreased neurologic event rate, data supporting this contention are lacking.[115]

Hypersensitivity to aspirin is encountered in clinical practice, typically manifesting as either a skin rash, urticaria, angioedema, or asthma. Anaphylactic shock is rarely observed, with an overall incidence of approximately 0.5%.[147]

The safety profiles of other antiplatelet agents, particularly when used in combination with thrombolytic therapy, are currently under investigation.[148]

COMBINATION THERAPY

The pathophysiology of arterial thrombogenesis provides a sound rationale for combining thrombin antagonists and antiplatelet agents with thrombolytic therapy. The most widely investigated combination, heparin and aspirin, provides a modest beneficial effect, reducing recurrent infarction, vascular mortality, and other thromboembolic events.

Despite an observed benefit, however, the risk of hemorrhagic events may be increased, particularly in patients undergoing invasive procedures (Table IV). The concomitant use of aspirin has long been identified as a risk factor for heparin-induced bleeding.[95] In ISIS-2,[115] the risk of both minor and major hemorrhage tended to correlate with the clinicians' intention at the beginning of the patients' hospitalization to use heparin therapy. In the GISSI-2/International Study[58,59] and in ISIS-3 (unpublished data), the addition of heparin to thrombolytic therapy and aspirin increased both minor and major bleeding, particularly among patients receiving streptokinase.[58] Patients were also at increased risk for intracranial hemorrhage (ISIS-3, unpublished data).

Unfortunately, the subcutaneous heparin regimen employed, coupled with the absence of anticoagulation monitoring in the GISSI-2/International Study and ISIS-3 trials prevents a clear understanding of the overall clinical impact of combination therapy. The findings of TIMI-II[96] suggest, however, that patient risk can be minimized by adjusting heparin administration to avoid activated partial thromboplastin times >2.5 times the control. The GUSTO trial will provide further insights into the risks and benefits of combined heparin, aspirin, and thrombolytic therapy.

TABLE IV Hemorrhagic Events in Patients Receiving Thrombolytic Therapy and Heparin (Randomized Trials)

Trial	Hemorrhagic Event	Heparin (%)	No Heparin (%)
GISSI-2	Major bleeding	1.0	0.6
	Minor bleeding	9.6	5.3
	Hemorrhagic stroke	0.3	0.3
International Study	Major bleeding	1.0	0.5
	Hemorrhagic stroke	0.3	0.4
Combined experience	Major bleeding	1.2	0.6
ISIS-3	Any bleeding	6.4	3.9
	Major bleeding	1.1	0.8
	*Hemorrhagic stroke	0.6	0.4

*Probable.
See Table I for abbreviations.

FUTURE DIRECTIONS

The basic framework on which thrombolytic and antithrombotic therapy for AMI is based states that: (1) arterial thrombosis, occurring at a site of atheromatous plaque rupture, is the proximate cause of coronary occlusion and myocardial tissue damage; (2) the greatest clinical benefit is achieved by restoring arterial reperfusion promptly; (3) the benefits of early reperfusion are sustained if arterial patency can be maintained; and (4) early reperfusion and maintained patency must be accomplished with minimal risk to the patient.

At the present time, a more complete understanding of thrombolytic resistance and coronary reocclusion has fostered the implementation of conjunctive therapeutic regimens, typically including both a thrombin antagonist and antiplatelet agent. Although the combined administration of heparin and aspirin has proven benefits, further reductions in thromboembolic events and patient mortality will likely require more potent and specific preparations.

The pivotal role of thrombin in arterial thrombogenesis suggests that an effective thrombin antagonist, combined with a fibrin-specific thrombolytic agent, may suffice. To this end, further research with r-hirudin (and its derivatives), argatroban, and possibly nonheparin glycosaminoglycans[149] should continue. It is possible, however, that generalized platelet inhibition will still be required to

neutralize the profound procoagulant state caused by plaque rupture, mural thrombosis, residual stenosis, and the fibrinolytic agents themselves.

Future progress will be influenced directly by the development of: (1) a reliable animal model that predicts clinical outcomes (safety and efficacy); (2) a consistent, rapid and reproducible means to monitor systemic anticoagulation; and (3) predictive tests for defining hemorrhagic risk in individual patients.

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Fibrinolytic Parameters and Hemostatic Monitoring: Identifying and Predicting Patients At Risk for Major Hemorrhagic Events

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The use of thrombolytic therapy has dramatically altered the treatment of acute myocardial infarction and is rapidly spreading from large medical centers to community hospitals throughout the country. The widespread use of thrombolytic therapy will benefit a wide range of people, but the potential risks of this form of therapy must be understood. Hemorrhage is one of the major risks of thrombolytic therapy. This review will focus on the data available from a number of recent, large trials of thrombolytic therapy for acute myocardial infarction with respect to laboratory parameters that may predict hemorrhagic complications and/or help with their management. We will discuss both conclusions drawn from currently available data and address future research directions.

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Thrombolytic therapy has proven to be a significant advance in the treatment of acute myocardial infarction. However, it is not without attendant problems. Chief among these is the risk of bleeding. Bleeding during the use of streptokinase in the early investigation of thrombolytics was attributed to the systemic lytic state caused by this agent. However, since the use of recombinant tissue plasminogen activator (rt-PA) has become more widespread, it has become clear that the systemic lytic state, infrequent with rt-PA, cannot be the sole cause of hemorrhagic events, since the hemorrhagic event rate with streptokinase and rt-PA is approximately the same.

This situation has become more complicated by the use of adjunctive therapy such as heparin or aspirin (for rt-PA), streptokinase, and other thrombolytic agents. Such adjunctive therapy, although important for limiting reocclusive events, has obvious implications for bleeding, since the purpose is to decrease the patient's ability to form blood clots.

In this section we will review the mechanisms of coagulation and fibrinolysis, highlighting new findings that may provide insight into monitoring strategies. Following this, we will detail the extent of the bleeding problem and review the general patient characteristics that appear to be associated with bleeding. Finally, we will illustrate the findings to date with conventional and new assays for factors associated with both coagulation and fibrinolysis, and conclude with our view of the current state of monitoring for patients at risk during thrombolytic therapy.

MECHANISMS OF FIBRINOLYSIS

Figure 1 illustrates, in a basic way, the key mechanistic concepts in fibrinolysis. Plasminogen activators such as rt-PA, streptokinase, and urokinase can directly or indirectly catalyze the conversion of plasminogen to plasmin in the fluid phase of blood. In addition, rt-PA can catalyze this conversion quite efficiently, on the fibrin surface.[1] In the

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fluid phase, the most important naturally occurring inhibitor is plasminogen activator inhibitor-1 (PAI-1), which inhibits rt-PA activity. The concentration of rt-PA in most individuals is approximately 5–20 ng/ml; the plasma concentration of PAI-1 is approximately 3–50 ng/ml.[2] Therefore, one would anticipate that under normal circumstances PAI-1 would have a strong influence on rt-PA activity, and, in fact, it has been reported that most of the circulating rt-PA exists in a complex with PAI-1.[2] However, during the course of thrombolytic therapy, the plasma concentration of rt-PA often reaches ≥1,000 ng/ml.[3] Under these conditions, one would anticipate that PAI-1 would not exert a significant influence, and in fact this appears to be the case. A recent report from the Thrombolysis and Angioplasty in Acute Myocardial Infarction (TAMI-I) experience indicated no significant association of PAI-1 with bleeding events or with other clinical outcomes, with the exception of a weak association between low PAI-1 antigen levels and patency at 90 minutes.[4]

Streptokinase does not have a plasma inhibitor under normal circumstances, but some individuals have circulating antibodies to streptokinase, which can be inhibitory.

Once plasmin is formed in the fluid phase, α_2-antiplasmin is a potent inhibitor that comes into play. However, this inhibitor does not function as efficiently when plasmin is present on the fibrin surface.[5] Fluid phase plasmin that is active (either for a brief time before becoming inactivated by α_2-antiplasmin, or because the α_2-antiplasmin reserve has been exhausted by extensive plasmin generation) is capable of partitioning to the fibrin surface and catalyzing fibrinolysis. However, plasmin may remain in the fluid phase and catalyze fibrinogenolysis and degrade Factors V and VIII, leading to decreased ability to generate thrombin. These latter activities, if left unchecked, lead to the so-called "systemic lytic state."

Another consequence of extended plasmin activity in plasma is the generation of fibrinogen degradation products, which may be capable of interrupting platelet aggregation or causing the production of weak fibrin clots.[6,7] Although much speculation has appeared in the literature concerning the possible anticoagulant effects of fibrinogen degra-

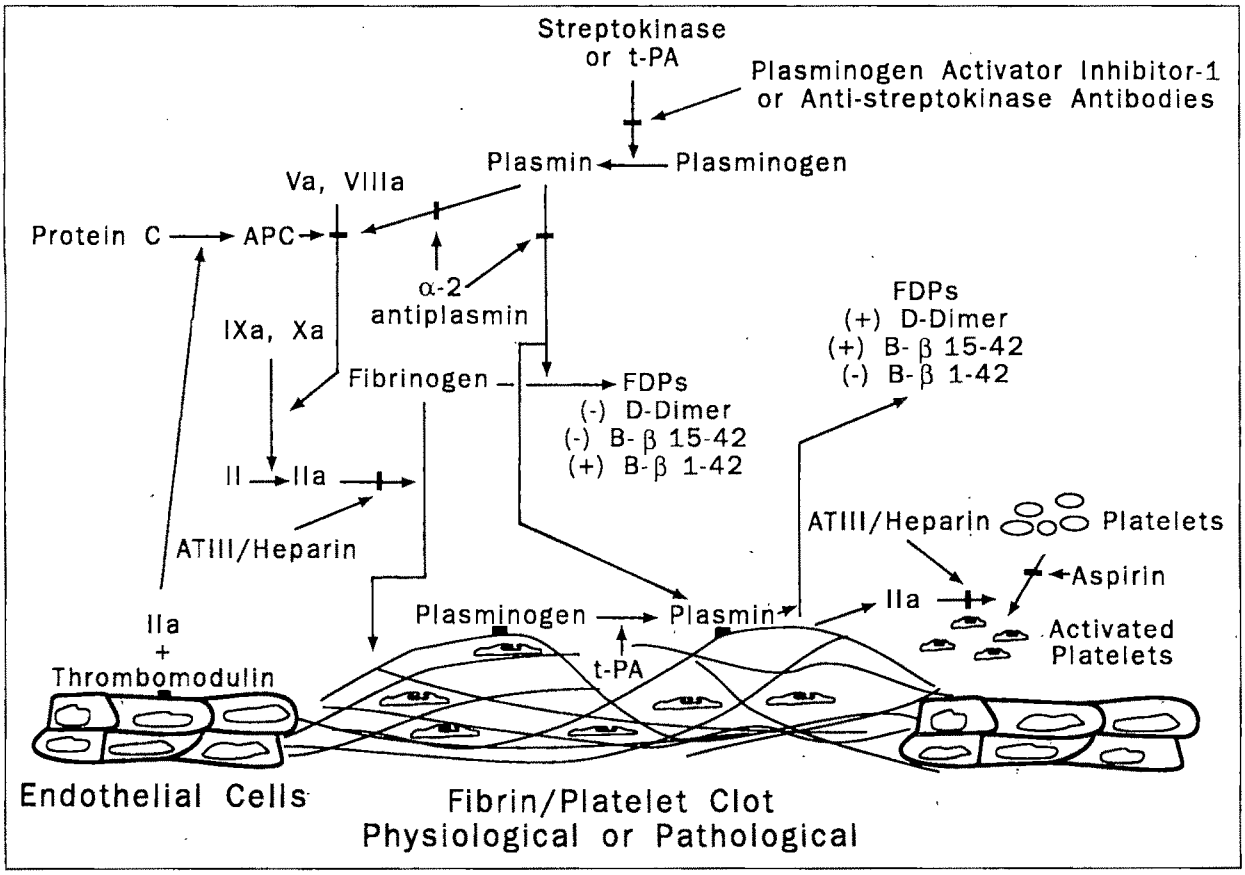


FIGURE 1. A basic schematic of several of the key concepts in thrombolysis. APC = activated protein C; II and IIa=prothrombin and thrombin; ATIII = antithrombin III; FDPS = either fibrin or fibrinogen degradation products; t-PA = tissue plasminogen activator; Va and VIIIa=Factors Va and VIIIa of the coagulation system. Bars across arrows indicate negative influences; arrows that point to such bars indicate factors that cause such influences; other arrows indicate factors that promote the indicated reaction.

dation products, there is little direct experimental evidence to support this position.

The lysis of the fibrin or platelet clot (fibrinolytic therapy appears to be much more effective against clots that have a substantial amount of fibrin associated with them, compared with clots that are primarily platelet plugs[8]) leads to the generation of fibrin degradation products of many types.[7,9] Among them is the D-dimer, so-termed because the cross-linking of the fibrin strands by Factor XIII cross-links 2 fibrin "D" domains, which remain cross-linked after plasmin-mediated lysis. (The fragments of fibrinogen generated by plasmin-mediated lysis are also called fibrinogen degradation products but do not contain the D-dimer.) The lysis of the fibrin-containing clot may also liberate a considerable amount of thrombin, which had been bound into the clot during its formation.[10] The exact role of this thrombin is not understood, but it is reasonable to assume that it functions as newly generated thrombin might function.

This leads us to the potential key role played by thrombin in this process. Although thrombolytic therapy may lead to the lysis of the occlusive blood clot and the reestablishment of perfusion, the underlying prothrombotic influences, such as the atherosclerotic surface or possible genetic predisposition, still remain. The high rate of reocclusive events that take place following successful thrombolysis with either rt-PA or streptokinase (recent estimates are 14–17%[11]) indicates how prothrombotic the situation actually is following thrombolysis. Adjunctive heparin therapy is still debated, but many are convinced that heparin is necessary to decrease the risk of reocclusion, and possibly to aid in the initial fibrinolytic process.[12] The danger, of course, is that by limiting thrombin activity and thrombin generation (through inhibition of Factor Xa), heparin may lead to hemorrhage.

Thrombin inhibition may be important in limiting platelet activation as well, since thrombin is a well-known platelet activator, even of aspirin-inhibited platelets,[13,14] and either newly formed thrombin or thrombin released from clots via fibrinolysis may lead to activation at the site of the occlusive clot. Again, however, if thrombin is a major platelet activator at the site of wounds, overheparinization might well lead to the inability to form platelet aggregates in primary hemostasis and, therefore, bleeding.

Finally, thrombin also works, in a sense, as an anticoagulant, through the activation of protein C in the thrombin–thrombomodulin complex.[15] Activated protein C, in concert with the other naturally occurring vitamin K-dependent anticoagulant protein S, works to limit thrombin generation by inactivation of activated Factor V. Although the activity of thrombin as a procoagulant appears to be primary, its other activities such as protein C activation should not be discounted, as we attempt to understand the complete series of events that accompany the application of thrombolytic therapy.

In summary, it appears that there are 2 main situations in which thrombolytic therapy may be associated with hemorrhage. In both cases, the activation of the fibrinolytic mechanism and disturbances in coagulation may be mechanistically involved.

Lysis of preexisting physiologic blood clots: In this situation a previous hemorrhage has been sealed off by proper hemostasis. An example might be a lesion in the vasculature of the intestine, or a small lesion in the cerebral vasculature. When thrombolysis is begun, not only is the occlusive coronary thrombus lysed, but the other, normal and protective, hemostatic plug is lysed as well. Under some circumstances, lysis is never complete and clinical bleeding does not occur. However, at times the lysis causes hemorrhage. It is possible that this latter event may be more common with high doses of rt-PA compared with streptokinase, since rt-PA is more efficient than streptokinase in lysing clots.[16] There may also be situations with either thrombolytic agent when it is impossible to achieve coronary thrombolysis without also lysing a physiologic clot and reestablishing a previous hemorrhage site. Also, a physiologic clot may be more fibrin rich than the clot obstructing the coronary artery, and therefore more susceptible to thrombolysis.[8] Unfortunately, in many cases it is difficult to establish whether preexisting physiologic clots are present, although a thorough clinical history is useful.

In any event, once a physiologic clot has been lysed and hemorrhage occurs, it is still possible that hemostasis will once again limit the amount of blood loss, and a second physiologic clot will be established at the same site. However, with the anticoagulation effects of plasmin's degradation of Factor V, Factor VIII, and fibrinogen (and possibly other effects), and the anticoagulants heparin and aspirin given as adjunctive therapy, hemostasis may have been compromised to the extent that bleeding can no longer be controlled.

Failure to achieve hemostasis when a vascular lesion occurs during thrombolysis: This second situation is very much like the first, with the

exception that it is not necessary to assume preexisting vascular damage has been limited by proper hemostasis. Instead, it is postulated that a vascular lesion occurred during the several hours of thrombolytic therapy, or during the immediate period following thrombolysis when coagulation remains compromised. In this scenario the effects of plasmin on the procoagulant system, and the effects of antithrombotic adjunctive therapy, seem to be paramount. Of course, it remains possible that rt-PA, streptokinase–plasminogen, or plasmin itself, may have as yet undiscovered activities toward the vascular wall, or certain (relatively) intact sections of it (possibly some forms of atherosclerotic plaque or areas of amyloid depositions), which might lead directly to hemorrhage, but this remains speculative.

The physiologic changes associated with the trauma of coronary thrombosis, infarction, and thrombolysis may well participate in producing hemorrhages if sections of the vasculature are already compromised. We have recently described the presence of amyloid deposits in the cerebral vasculature of a patient with a fatal central nervous system hemorrhage following rt-PA administration.[17] We speculate that such deposits may be common in older individuals and may be associated with an increased frequency of hemorrhage by either of the mechanisms described previously. If true, this may explain at least part of the age association of hemorrhagic events during thrombolysis (see later). The anatomic location of the bleeding events in the central nervous system in Thrombolysis in Myocardial Infarction (TIMI-II) is consistent with an association with amyloidotic deposits.[18]

Since the above scenarios all involve the major factors of both hemostasis and fibrinolysis, it seems reasonable to hypothesize that evaluation of these systems, either before, during, or after thrombolysis, might lead to the uncovering of plasma markers that could help to discriminate between those individuals who are going to have hemorrhagic events and those who are not. We and others have been involved with clinical research to explore this hypothesis, and some results will be detailed.

Hemorrhagic events—the extent of the problem: Table I lists the rates of major and central nervous system hemorrhagic events in many of the large clinical trials in which these data have been collected.[3,19–30] It should be pointed out that there are several important limitations with tabulations such as this.[31,32] In essence, many of the studies fail to meet all the following criteria: (1) a clearly defined cohort of patients under treatment; (2) prospectively characterized definitions of bleeding that were applied consistently across the cohort; and (3) a statistically appropriate number of patients. Nonetheless, we believe that several messages are clear from an inspection of Table I.

TABLE I Frequency of Hemorrhagic Events in Large Scale Clinical Trials of Thrombolytic Therapy

Study	Treatment	Major Events (%)	CNS Events %	n
Streptokinase				
ECSG[21]	Streptokinase	1.3	1.3	156
	Placebo	0.6	0.0	159
GISSI-1[19,38]	Streptokinase	0.3	0.8	5,860
	Control	—	0.7	5,852
ISAM[20]	Streptokinase	5.9*	0.5	859
	Control	1.5	0.0	882
White et al[23]	Streptokinase	1.0	0.0	107
	Control	—	0.0	112
ISIS-2[24]	Streptokinase	0.5	0.1	8,490
	Placebo	0.2	0.0	8,491
AIMS[30]	APSAC†	3.8	1.3	624
	Control	2.2	0.6	634
rt-PA				
ASSET[25]	rt-PA	1.4	0.3	2,512
	Placebo	0.5	0.1	2,493
TAMI[27]	rt-PA	19	0.5	386
Simoons et al[26]	rt-PA	4.0	0.5	184
	rt-PA + PTCA	10.0	0.5	183
TIMI-II (100 mg)[3]	rt-PA (conservative)	4.2	0.3	1,395
	rt-PA (invasive)	7.0	0.4	1,424
TIMI-II (150 mg)	rt-PA (conservative)	8.5‡	1.5	263
	rt-PA (invasive)	—	1.9	257
Comparison				
TIMI-I[28]	Streptokinase	15.6	0.0	147
	rt-PA	15.4	0.0	143
GISSI-2[22]	Streptokinase	1.0	0.25	6,199
	rt-PA	0.5	0.3	6,182
International Study Group[23]	Streptokinase	0.8	0.4	4,197
	rt-PA	0.7	0.6	4,190

*Data include total number of hemorrhagic events, not just "major" events.
†Data include all strokes (not just hemorrhagic); bleeding events include gastrointestinal bleeding and bleeding requiring transfusion.
‡Includes both "conservative" and "invasive" patients.
AIMS = APSAC Intervention Mortality Study; APSAC = anisoylated plasminogen-streptokinase activator complex; ASSET = Anglo-Scandinavian Study of Early Thrombolysis; ECSG = European Cooperative Study Group; GISSI-1 = Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico; GISSI-2 = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; ISAM = Intravenous Streptokinase in Acute Myocardial Infarction; ISIS-2 = Second International Study on Infarct Survival; PTCA = percutaneous transluminal coronary angioplasty; rt-PA = recombinant tissue plasminogen activator; TAMI = Thrombolysis and Angioplasty in Acute Myocardial Infarction; TIMI-I [II] = First [Second] Thrombolysis in Myocardial Infarction.

There is a wide range in reported "major hemorrhagic events." This most likely reflects whether invasive procedures were a part of the standard protocol and differing criteria for "major" events.

Recently Fennerty et al[31] reviewed bleeding events in major clinical trials and reported that, for streptokinase (with a total patient group of approximately 15,000), the incidence of major bleeding was approximately 1%, with central nervous system bleeding being 0.15%. In studies with invasive procedures, however, the incidence of major hem-

orrhage was 7–19%, the increase caused primarily by the invasive procedures themselves.

Concerning rt-PA, the largest experience is in TIMI-II,[3] Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2),[22] and the International Study Group.[29] The criteria used in TIMI-II to classify a patient as having had a major hemorrhagic event were intracranial hemorrhage or cardiac tamponade, or a decrease in hemoglobin concentration of ≥ 50 g/liter, regardless of whether a site of loss was identified. Also, a separate committee reviewed all deaths in TIMI-II, and patients were classified as having had a major hemorrhagic event if the death was due to hemorrhage. Using these criteria, major hemorrhages occurred in 4.2% of the patients receiving 100 mg rt-PA and 8.5% of the patients receiving 150 mg t-PA, both groups in the "conservative strategy" arm of TIMI-II. (TIMI-II had 2 arms, a conservative strategy arm with percutaneous transluminal coronary angioplasty only if clinically indicated, and an invasive strategy arm, with either immediate or delayed percutaneous transluminal coronary angioplasty as part of the protocol.) This illustrates that bleeding is responsive to rt-PA dose, at least as measured in large populations. Comparing the invasive to the noninvasive arm, at 100 mg t-PA, the major hemorrhagic rates were 7.0% and 4.2%, respectively, pointing out the dependence of bleeding on invasive procedures. The results may be compared with those seen in TIMI-I, where the bleeding rate for 80 mg rt-PA was estimated at 15.4%. This value appears high, but almost certainly reflects the early invasive procedures that were performed during TIMI-I.

The GISSI-2 group has reported that major hemorrhagic events occurred in 0.5% of the patients receiving rt-PA and 1.0% of the patients receiving streptokinase[22]; the companion International Study Group trial reported major hemorrhagic events in 0.7% of the rt-PA patients and 0.8% of the patients receiving streptokinase.[29] Both studies were 2×2 factorial in design, where heparin was examined as well. The combined data for heparin indicated 1.0% major bleeding events with heparin and 0.5% without.[29]

In studies where the sites of bleeding have been reported, the most common site of bleeding was the catheterization site used for coronary angiography (or other puncture site); for example, in the TIMI-II conservative arm, 39% of the major hemorrhages occurred at the catheterization site or other puncture sites,[3] and in TIMI-I puncture sites were responsible for >70% of the major bleeding events.[28]

As mentioned previously, the most worrisome aspect of bleeding during thrombolytic therapy is central nervous system hemorrhage. As seen in Table I, a broad range has been reported, from 0% in the streptokinase study of White et al[23] and in the streptokinase and rt-PA arms of TIMI-I,[28] to 1.9% in the invasive arm (150 mg rt-PA) of TIMI-II.[3] It is difficult to ascribe accuracy to the smaller studies, so it appears likely that the optimal rate for rt-PA is approximately the 0.3% rate achieved in the conservative arm of TIMI-II, using 100 mg rt-PA. The combined data from GISSI-2 and the International Study Group trial (>10,000 patients each, in the rt-PA and streptokinase arms) indicate an overall stroke rate that slightly favors streptokinase, although the hemorrhagic stroke rate and overall mortality were not different.

In any event, it is clear that central nervous system hemorrhage and major bleeding events are not uncommon in patients receiving thrombolytic therapy and are increased in frequency with higher doses of thrombolytic agent (at least for rt-PA), and possibly with invasive procedures such as percutaneous transluminal coronary angioplasty and coronary angiography.

PREDICTORS OF HEMORRHAGE

Coronary angiography and percutaneous transluminal coronary angioplasty are major risk factors for bleeding during thrombolytic therapy.[3,31] It also appears that the use of heparin is associated with increased bleeding.[3] In the 2 large European studies where there is a direct comparison of heparin versus no heparin, there was a small but significant increase in "major" bleeding in the heparin group, and, in at least 1 study (ISIS-3), an increase in the number of hemorrhagic strokes. The use of aspirin, in doses given in the Second International Study of Infarct Survival (ISIS-2) trial, does not appear to be associated with an increased risk of major bleeding or hemorrhagic stroke.[24]

Age appears to be a risk factor for bleeding, although the results have been inconsistent.[3,31,33] Multiple logistic regression analysis of the TIMI-II data revealed that age was associated with bleeding in the invasive strategy group, but not in the conservative strategy group. The lack of association in the conservative strategy group may be due to the relatively small number of bleeding events in this group. A weak association of age with bleeding has also been reported by the TAMI investigators.[34]

Univariate analysis of data from the TIMI-II

study revealed that bleeding (major or minor) was significantly associated with female gender and weight (<70 kg vs >70 kg).[3] These relations remained in multivariate analysis as well. However, the associations did not reach statistical significance when only major events were considered. Again, results from the TAMI experience with rt-PA are consistent with there being weak but significant associations between bleeding and both weight and female gender. The relation with weight is confounded by the fixed dosage regimens used in most studies and argues for a weight-adjusted dosing regimen.

Much has been made in the past of the lytic state and its relation to bleeding. However, as already discussed, most now believe that hemorrhagic events are caused by the local action of plasmin, rather than as a direct consequence of a systemic lytic state. Measurements that have been proposed as possible markers of bleeding are listed in Table II. Some of these have been adequately evaluated in large clinical trials, and others have not. We will review the results to date.

Although extreme hypofibrinogenemia has been associated with bleeding,[7] many hemorrhagic events during thrombolytic therapy are not associated with fibrinogen breakdown.[3] On the other hand, results from the TAMI investigators and from TIMI-II (comparing the 150 mg and 100 mg doses of rt-PA) illustrate that increased bleeding is associated with increased fibrinogenolysis in large scale studies.[3,34] It seems clear that fibrinogen loss, in most cases, is a marker for plasmin activity, but as such does not itself contribute to bleeding unless very low levels are achieved. Although it is possible that the fibrinogen degradation products produced by plasmin may have an anticoagulant role to play (see previous discussion), it appears that most likely it is other, more direct actions of plasmin that are the proximate cause of bleeding during thrombolytic therapy.

A review of the results of the TIMI-II trial[3] illustrates our current knowledge about the relations of plasmin markers and bleeding events; the data from other, smaller studies such as TIMI-I and the TAMI studies[28,34] are consistent with the TIMI-II results. Univariate analysis (of data from the conservative strategy, 100 mg rt-PA arm) revealed significant relations between bleeding and peak plasma rt-PA levels and fibrinogen loss (i.e., fibrinogen values of ≤100 mg/dl at 5 hours into the 6-hour infusion). The relation to fibrinogen loss was significant, however, only when major and minor bleeding events were included in the analysis; the association with peak rt-PA concentration was true for major and minor bleeding events, or for major events alone. There was also a weak, but significant, association between fibrinogen degradation product values at 5 hours and bleeding events.

TABLE II Potential Markers of Hemorrhage in the Setting of Thrombolytic Therapy

Marker	Activity
Fibrinogen loss	Plasmin activity
Fibrinogen degradation product generation	Plasmin activity
Plasminogen loss	Plasmin generation
Peak tissue plasminogen activator level	Potential for plasmin generation
D-dimer	Plasmin activity against fibrin
B-β 1–42	Plasmin activity against fibrinogen
B-β 15–42	Plasmin activity against fibrin II (uncross-linked fibrin)
Bleeding time	Primary hemostasis
Platelet count	Primary hemostasis

When hemorrhagic stroke alone was considered, there were no significant associations with fibrinogen, fibrinogen degradation products, plasminogen or peak rt-PA levels. Just as with major bleeding events, however, there was an increase in hemorrhagic stroke in the rt-PA 150 mg arm of TIMI-II. The decrease in major hemorrhagic events accompanying the change from 150 mg to 100 mg was constituted almost entirely by a drop in the hemorrhagic stroke rate. As already mentioned, this is consistent with the hypothesis that rt-PA may have a direct effect on certain vasculature, possibly including cerebral vessels. However, this observation must be tempered by the fact that patient entry criteria and aspirin dosing were also modified when the dose was reduced.

These results from the TIMI-II trial confirm results reported in other smaller trials and lead to the conclusion that currently the "standard" measurements of coagulation and fibrinolysis (i.e., fibrinogen, fibrinogen degradation products, plasminogen, and rt-PA), although under certain conditions associated with bleeding, do not offer the sensitivity and specificity that are required for routine use for prediction of bleeding among individual patients. There are several possible explanations for this. As already mentioned, fibrinogen rarely reaches levels low enough to be a significant cause of bleeding itself. One might consider the peak rt-PA level a possible marker for plasmin generation, but we speculate that circulating rt-PA values are themselves only pale reflections of the fibrin-bound, catalytically active rt-PA that might exist in any individual. Total fibrin burden, differences in elimination rates, fibrin location in the vasculature, and other variables all might contrib-

ute to a heterogeneous set of responses to a given rt-PA dose, even when adjusted by weight. Of course, the presence or absence of preexisting lesions may well be the major factor in bleeding events not associated with invasive procedures.

The loss of plasminogen might be considered a potentially useful marker of plasmin generation, but in TIMI-II plasminogen loss was not associated with bleeding. There was a moderate correlation of plasminogen to rt-PA values, $r = -0.33$, $p < 0.001$. Finally, fibrinogen degradation product measurements might also be candidate markers of plasmin activity. However, since fibrinogen degradation product measurements in the setting of thrombolytic therapy primarily reflect fibrinogenolysis and not fibrinolysis (see later), they are essentially equivalent to "fibrinogen loss."

OTHER ASSAYS OF COAGULATION AND FIBRINOLYSIS

There are several other potential markers of hemorrhage that have been explored in the setting of thrombolytic therapy (Table II). We and others have evaluated the potential for the use of D-dimer measurements and measurements of the B-peptides.[35] Concerning D-dimer, most assays that have been evaluated for this measurement do not have sufficient specificity, in the setting of considerable fibrinogenolysis, to reflect D-dimer levels accurately.[35] Instead, many of the presently available D-dimer assays demonstrate cross-reactivity with noncross-linked fibrinogen degradation products during the plasmin-mediated digestion of fibrinogen, which occurs even with rt-PA, and occurs extensively with non–fibrin-specific agents such as streptokinase. We are currently evaluating the use of a specific D-dimer assay,[35] using samples collected during TIMI-II, to determine if this measurement is useful in the context of hemorrhage prediction or prediction of other clinical events.

Assay of B-β 15–42 peptide levels might also reveal information about plasmin activity, but again the specificity of the commercial assay is not adequate when a large amount of the peptide B-β 1–42 is being produced, as occurs during thrombolytic therapy.[35] The B-β 1–42 assay itself, which does not have cross-reactivity problems, might prove to be a useful marker of plasmin activity; these studies are currently underway using frozen TIMI-II samples.

It has been proposed that monitoring the bleeding time might be useful for prediction of hemorrhagic events.[36] However, although a significant relation has been observed between hemorrhagic events and prolongation of the bleeding time, the weak nature of this relation precludes its usefulness for individual patients. The bleeding time holds a unique place in clinical assessment of bleeding potential, since it is widely used in a variety of settings, yet objective evidence that might support this use has not been established.[37]

Thrombocytopenia following the use of rt-PA has been observed in both TIMI-I and TIMI-II.[3,28] In TIMI-II, there was a pronounced drop in platelet count for the first 5 days following therapy, with a rebound to normal levels over the next 5 days. This drop was approximately the same for both the 100 mg and 150 mg arms, which, taken together with the timing, suggests that heparin played a significant role. Patients with platelet counts $< 100 \times 10^9$/liter had a 7.5-fold greater risk of bleeding than those with higher platelet counts. This is one of the strongest markers of bleeding potential we have observed and approaches being of clinical utility. If the platelet loss reflects primarily heparin levels, this suggests that direct heparin measurements may be of utility. We are currently performing such measurements on the frozen samples from TIMI-II to evaluate this hypothesis.

In summary, we do not at this time have assays that are clinically useful for the prediction of bleeding in individuals treated with thrombolytic agents. Although there is controversy concerning the use of such agents in patients of advanced age, weak associations with female gender and low body weight do not preclude the use of thrombolytic agents in thin women. These results primarily argue for weight-adjusted dosing regimens. Plasma coagulation protein measurements also provide weak associations, but do not appear to have predictive value for individual patient management. Platelet counts, however, should be monitored, because low values have one of the strongest correlations with hemorrhagic events yet observed. New assays are currently being evaluated, and data will be available soon.

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Thrombolytic Therapy: Adjuvant Mechanical Intervention for Acute Myocardial Infarction

David W.M. Muller, MBBS, and Eric J. Topol, MD

Following successful pharmacologic thrombolysis, early coronary angiography frequently shows a tight residual stenosis in the infarct-related artery at the site of recent occlusion. Approaches to the management of the residual stenosis have undergone a gradual evolution from an aggressive strategy of immediate balloon dilation to a more conservative approach. Randomized, controlled trials have indicated that immediate percutaneous transluminal coronary angioplasty (PTCA) is associated with no greater recovery in regional or global left ventricular function, and a tendency toward an increased incidence of complications, including the need for emergency coronary artery surgery and blood transfusion. The role of immediate rescue PTCA for failed thrombolysis has not been as rigorously investigated, but selected patients, including those with evidence of ongoing myocardial ischemia or hemodynamic instability, may benefit from this approach. A major source of current controversy is the value of routine coronary angiography after uncomplicated myocardial infarction. Two carefully conducted trials have indicated that a conservative strategy of clinically indicated, predischarge cardiac catheterization may be associated with an increased need for readmission and late, elective cardiac catheterization when compared with a more invasive strategy of routine coronary angiography, but that the conservative approach is not associated with an increased incidence of death or reinfarction. Provision was not made in these studies, however, for evaluating the positive economic and psychologic impact of early coronary angiography, early hospital discharge, and early return to work of patients with a favorable postinfarction prognosis. It is concluded that early mechanical revascularization following thrombolysis should be considered for ongoing myocardial ischemia, but should otherwise be deferred pending the results of predischarge functional studies. For most patients, routine coronary angiography is likely to remain an important diagnostic tool and an integral component of the management of the convalescent phase of acute myocardial infarction.

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Data accumulated in recent years have suggested strongly that both in-hospital and long-term survival after acute myocardial infarction can be increased significantly by measures that achieve early and sustained patency of the infarct-related coronary artery.[1–6] Thrombolytic therapy is one means of effectively restoring antegrade coronary flow in a high proportion of treated patients. Thrombolysis alone does little, however, to alter the underlying vessel wall disease that precipitated the acute ischemic event. As a result, infarct vessel reocclusion is relatively common and is associated with a high incidence of adverse clinical outcomes.[7] In an attempt to reduce the likelihood of recurrent myocardial ischemia and to facilitate left ventricular functional recovery after myocardial reperfusion, mechanical revascularization therapies, including coronary balloon angioplasty and coronary artery bypass grafting, have been systematically evaluated by many investigators as adjuncts to pharmacologic thrombolysis.

In 1982, Meyer and colleagues[8] described the use of percutaneous transluminal coronary angioplasty (PTCA) to dilate high-grade residual coronary stenoses after successful thrombolysis. In this small retrospective study, PTCA was attempted in 21 patients between 20 minutes and 31 hours after intracoronary administration of streptokinase. The procedure was successful in 17 patients; there were no in-hospital reocclusions and the late follow-up period was characterized by a low incidence of recurrent myocardial ischemia. In contrast, recurrent myocardial infarction occurred during the

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initial hospitalization in 4 of 18 patients treated medically after intracoronary thrombolysis, and 3 patients died during the follow-up period.[8] Early surgical revascularization following successful intracoronary thrombolysis for evolving myocardial infarction was also reported to be associated with a favorable long-term outcome by Mathey and colleagues.[9] These 2 studies focused attention on the possibility of a combined pharmacologic and mechanical approach to restoring and maintaining antegrade coronary flow as the definitive treatment for acute myocardial infarction. In the intervening 10 years since the publication of these reports, the use of thrombolytic therapy has become firmly established as the first line of therapy for a substantial proportion of patients,[10] but the need for, and optimal timing of, adjuvant mechanical revascularization to prevent late complications in this population remains somewhat controversial. Several postthrombolytic revascularization strategies have been examined in multicenter, randomized, controlled trials. These include PTCA immediately after successful thrombolysis or for thrombolytic failure, late (usually predischarge) PTCA of residual critical stenoses in patent infarct-related arteries, and selective PTCA, in which mechanical revascularization is reserved for patients with recurrent, spontaneous or stress-induced postinfarction myocardial ischemia.

THROMBOLYSIS AND IMMEDIATE PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY

The role of balloon dilation of residual coronary stenoses in patent arteries immediately after successful thrombolysis has been well studied in randomized, controlled clinical trials. Three large trials compared immediate PTCA with a deferred interventional strategy in patients who had received intravenous recombinant tissue plasminogen activator (rt-PA).[11–13] Although the underlying hypothesis was the same for each of the studies, there were several important differences in study design among the trials. In the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) trial,[11] patients presenting within 4 hours of symptom onset underwent diagnostic coronary angiography 90 minutes after the initiation of the thrombolytic infusion. Only those patients with patent infarct vessels and anatomy deemed suitable for PTCA were then randomized to immediate coronary angioplasty or to repeat cardiac catheterization and PTCA prior to hospital discharge. In the Thrombolysis in Myocardial Infarction (TIMI-IIA) study,[12,13] randomization to 1 of 3 treatment strategies was performed prior to coronary angiography. Immediate PTCA (including dilation of persistently occluded arteries), was compared first with deferred coronary angiography and PTCA of suitable stenoses, performed 18–48 hours after the administration of thrombolytic therapy, and second, with a conservative strategy that consisted of predischarge coronary angiography in all patients and PTCA only in patients with exercise-induced ischemia and appropriate coronary anatomy. In the European Cooperative Study Group (ECSG) trial,[14] eligible patients were randomly allocated either to a strategy of immediate coronary angioplasty, including PTCA of persistently occluded arteries, or to a strategy in which coronary angiography without PTCA was performed 10–20 days after admission. Because of these differences in study design, there were important differences between the trials in the frequency with which mechanical revascularization was actually performed. Coronary angioplasty was attempted in 100% of patients randomized to the immediate PTCA group in TAMI, compared with 72% in TIMI-IIA and 92% in ECSG. Similarly, in the deferred intervention groups, PTCA was performed in 52% of the patients in TAMI, but in 55% in TIMI-IIA and 6% in ECSG.

Despite these differences in trial design, the conclusions of the respective study groups were remarkably concordant. The principal end point for each study was left ventricular ejection fraction, determined by contrast ventriculography performed prior to hospital discharge. Each of the 3 trials concluded that immediate PTCA did not improve the extent of left ventricular global or regional functional recovery during the early convalescent period (Figure 1). Moreover, in each study, immediate intervention was associated with an increased incidence of procedural complications (including the need for emergency coronary artery bypass surgery and blood transfusion), no reduction in the incidence of reocclusion and reinfarction, and a trend toward an increased in-hospital mortality (Table I).

Studies of PTCA immediately after successful thrombolysis using agents other than rt-PA have also shown no significant advantage of this strategy over a deferred PTCA approach. Erbel and colleagues[15] randomly assigned 206 patients with acute myocardial infarction to immediate angioplasty or no PTCA after initial treatment with combined intravenous and intracoronary streptokinase and mechanical recanalization using a flexible guide

TABLE I Clinical Outcomes in the Trials of Intravenous Tissue Plasminogen Activator and Immediate Percutaneous Transluminal Coronary Angiography: Comparison of Immediate and Deferred Interventional Strategies

	TAMI (n = 386)	ECSG (n = 367)	TIMI-IIA (n = 389)
In-hospital mortality (%)			
Immediate	4	7	8
Deferred	1	3	5
Reocclusion (%)			
Immediate	11	12.5	—
Deferred	13	11	—
Emergency CABG (%)			
Immediate	7	3	5
Deferred	2	0	3
Blood transfusion (%)			
Immediate	21	10	11
Deferred	14	4	3

CABG = coronary artery bypass graft surgery; ECSG = European Cooperative Study Group; TAMI = Thrombolysis and Angioplasty in Myocardial Infarction Trial; TIMI = Thrombolysis in Myocardial Infarction trial.

wire. Coronary angioplasty was attempted in all but 2 of the patients assigned to immediate PTCA, including patients with complex coronary anatomy, but was considered to have been successful in only 69% of these attempts. No difference in clinical outcome or mortality was apparent after 3 years follow-up. Coronary reocclusion or reinfarction occurred in 18% of patients undergoing immediate PTCA compared with 29% in the conservatively treated patients (p = nonsignificant) and the 3- year survival rates were 80% and 78%, respectively.

POTENTIAL EXPLANATIONS FOR THE NEGATIVE IMPACT OF IMMEDIATE PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY

From the above studies, it appears that immediate PTCA after successful pharmacologic thrombolysis has no role in the routine management of acute myocardial infarction. Several explanations may account for the failure of this therapeutic approach. Conceivably, the results may be falsely negative because of the inclusion of inappropriate patients or the selection of insensitive end points or, alternatively, immediate PTCA may be truly detrimental and may actually promote adverse outcomes.

First, several trial design issues should be considered. One potential explanation for the lack of benefit of immediate mechanical revascularization in these studies may be that global and regional left ventricular function are insensitive endpoints that poorly reflect the potential impact of a therapy on long-term postinfarction survival.[3,16] Indeed, several studies have shown clearly that early myocardial reperfusion therapy may increase long-term survival in the absence of a demonstrable effect on left ventricular functional recovery.[1,17,18] In part, this lack of sensitivity may arise because patients selected for inclusion in the trials had well preserved global left ventricular function at presentation; the mean predischarge left ventricular ejection fraction for the 953 patients in the 3 rt-PA and immediate PTCA trials was 51%. A second possibility is that the duration of the initial follow-up period may have been inadequate to demonstrate improvement in left ventricular functional recovery and a reduction in late adverse events. However, careful assessment of late events and out-of-hospital survival of patients enrolled in the TIMI study[13] showed that at 6 weeks, no difference was apparent between the groups in resting left ventricular ejection fraction, peak exercise ejection fraction or infarct zone segmental ejection fraction (Table II). Similarly, clinical follow-up 12 months post infarction showed no difference in the cumulative incidence of recurrent myocardial infarction, the need for coronary artery bypass graft surgery or death, despite a considerable difference in the frequency with which coronary angioplasty was performed in the 3 groups (Table II). Finally, the inclusion of patients with noncritical residual stenoses may have obscured recognition of a positive impact of PTCA in patients with critical stenoses,

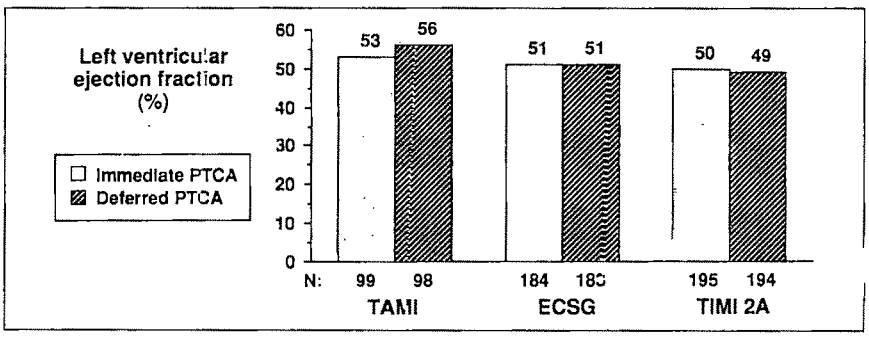


FIGURE 1. Predischarge left ventricular ejection in the immediate and deferred percutaneous transluminal coronary angioplasty (PTCA) groups of the 3 rt-PA/PTCA trials. Immediate PTCA was not associated with significant improvement in global left ventricular function in any of the trials. ECSG = European Cooperative Study Group; TAMI = Thrombolysis and Angioplasty in Myocardial Infarction trial; TIMI = Thrombolysis in Myocardial Infarction trial. (Adapted from *N Engl J Med*,[11] *JAMA*,[12] and *Lancet*.[14])

the group at greatest risk of reocclusion and in whom flow restriction is most likely to compromise left ventricular functional recovery.[19–22] This possibility was explored by Belenkie and colleagues[23] in a recent randomized study of immediate PTCA versus PTCA performed 18–48 hours after intravenous thrombolysis. In the study, the angiographic and left ventricular functional outcomes were stratified according to the adequacy of thrombolytic reperfusion and correlated with the incidence of reocclusion.[23] Ineffective reperfusion was defined as a residual lumen diameter stenosis >90% or delayed distal filling at the time of the initial diagnostic coronary angiogram. Reocclusion during the 18–48 hours before the scheduled angiographic procedure in patients assigned to the delayed PTCA strategy occurred in 37% of the patients with ineffective reperfusion compared with 5% of those with effective reperfusion ($p = 0.02$). Improvement in regional, but not global, left ventricular function was also greater in patients with initially ineffective reperfusion. However, neither the frequency of reocclusion nor the left ventricular functional recovery was influenced by whether PTCA was performed immediately or at 18–48 hours.[23]

More likely than any of the methodologic considerations mentioned is the possibility that balloon dilation is truly detrimental and actually incites further thrombus formation and reocclusion in patients with freshly disrupted atheromatous plaques, even in the presence of systemic fibrinogenolysis. The presence of an intraluminal thrombus is known to be a risk factor for abrupt occlusion during elective coronary angioplasty,[24–26] and for procedural failure in the setting of acute myocardial infarction.[27] Nonrandomized, retrospective studies have also suggested that elective balloon angioplasty performed within 1 week of symptom onset in patients with unstable coronary syndromes is associated with a lower success rate and a higher incidence of major procedural complications than a deferred PTCA strategy.[28] Several studies have described the histopathologic appearance of coronary arteries after sequential thrombolysis and balloon dilation in patients dying during the early postinfarction period.[29,30] In one study,[30] prominent intramural hemorrhage was noted at the site of balloon dilation, and in 1 patient, medial hemorrhage resulted in subtotal occlusion of the dilated vessel.

Whether immediate PTCA would become a valuable strategy if reocclusion could be prevented by more potent antithrombin and antiplatelet agents, or by other interventional procedures such as directional coronary atherectomy or laser balloon angioplasty, is at present unclear. This possibility was suggested by a recent retrospective analysis of the results of the ECSG trial.[31] The study examined the effects of immediate PTCA on left ventricular functional recovery in the subgroup of patients with successful reperfusion and sustained patency of the infarct artery. In these patients, global left ventricular function was somewhat better in the immediate PTCA group (left ventricular ejection fraction 50.8% vs 49.0%) due principally to a less extensive segment of regional infarct zone dysfunction.[31] At the present time, however, the potential hazards of these procedures appear to outweigh this relatively small benefit, and there do not appear to be any data to suggest that immediate PTCA should be performed routinely following successful thrombolysis, no matter how severe the residual coronary stenosis.

TABLE II Delayed, Elective Intervention and a Conservative Management Strategy after Thrombolysis

	TIMI-2B (n = 3,262)	SWIFT (n = 800)
Thrombolytic agent	t-PA	Anistreplase
Follow-up	6 weeks	1 year
Mortality (%)		
Invasive	5.2	5.8
Conservative	4.7	5.0
Reinfarction (%)		
Invasive	6.4	15.1
Conservative	5.8	12.9
Blood transfusion (%)		
Invasive	5.5	19.9*
Conservative	4.3	16.1*
Resting LVEF (%)		
Invasive	50.5	50.7
Conservative	49.9	51.7

LVEF = left ventricular ejection fraction; SWIFT = Should We Intervene Following Thrombolysis? trial; TIMI = Thrombolysis In Myocardial Infarction trial; t-PA = tissue plasminogen activator.
*Total hemorrhagic events.

RESCUE CORONARY ANGIOPLASTY

In contrast to the apparent consensus of opinion on the role of immediate PTCA of successfully recanalized infarct vessels, opinions on the importance of emergency balloon dilation of persistently occluded coronary arteries remain divergent, primarily because of a lack of relevant randomized data. Data from several observational studies do suggest, however, that rescue coronary angioplasty may be of value for thrombolytic failure in selected patients. The combined experience of rescue coronary angioplasty in the first 5 TAMI studies was recently reported.[32] In this retrospective analysis, the in-hospital and long-term outcomes of 607

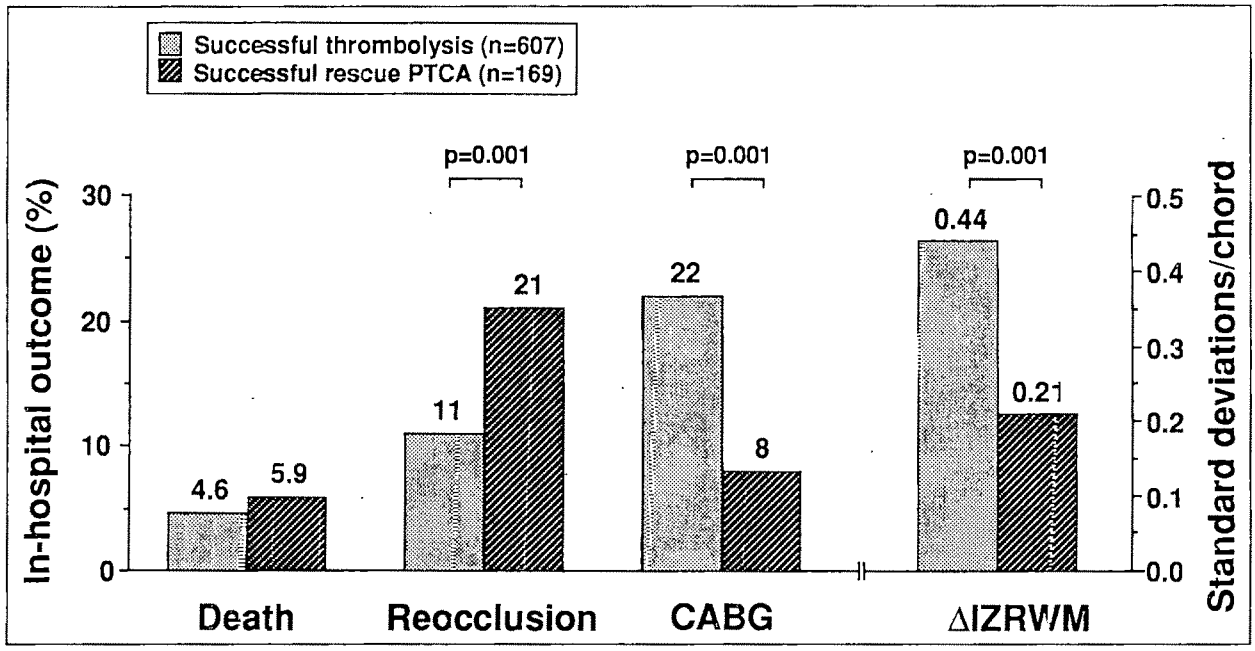


FIGURE 2. Successful pharmacologic thrombolysis versus successful rescue percutaneous transluminal coronary angioplasty (PTCA) after failed thrombolysis: In-hospital clinical outcome and regional infarct zone wall motion recovery (IZRWM). CABG = coronary artery bypass grafting. (Adapted from *J Am Coll Cardiol.*[32])

patients with successful thrombolysis were compared with the outcomes of 169 patients with successful rescue PTCA following failed intravenous thrombolysis. Although the overall in-hospital and long-term mortalities were similar in the 2 groups (4.6% vs 5.9% and 2% vs 3%, respectively), the incidence of reocclusion of the infarct-related artery was considerably higher following rescue angioplasty than following successful pharmacologic thrombolysis (21% vs 11%, $p < 0.001$) (Figure 2). This increased reocclusion rate was associated with significantly less improvement in both global and regional left ventricular functional recovery. Importantly, the incidence of reocclusion appeared to be markedly influenced by the thrombolytic regimen. Reocclusion after successful rescue PTCA occurred in 29% of patients treated with rt-PA alone, compared with 12% of patients treated with intravenous urokinase and 4% of patients treated with the combination of rt-PA and urokinase ($p < 0.019$). These findings are consistent with previous observations of a very high reocclusion rate following PTCA for unsuccessful rt-PA therapy[33] and lower, but nonetheless significant, reocclusion rates following the use of agents with more profound systemic fibrinolytic potential.[34–39] Several explanations have been offered for the high reocclusion rate after successful rescue PTCA.[32,40,41] Postmortem studies have suggested that atheromatous plaque at the site of acute occlusion in patients in whom pharmacologic thrombolysis has failed to restore luminal patency is characterized by more extensive fissuring and disruption, with a greater component of intramural, platelet-rich thrombus that is relatively resistant to systemic fibrinolysis. Balloon dilation may simply extend the intimal fissure and aggravate an already highly thrombogenic focus.

Data from the TAMI study group experience also suggest that failure of rescue angioplasty to restore infarct vessel patency may be associated with a considerably increased early postinfarction mortality.[32] Although the overall mortality of patients undergoing rescue PTCA was 9.9%, the in-hospital mortality following successful rescue PTCA was 5.9% compared with 39.1% in patients in whom the procedure failed to restore antegrade flow (Figure 3). Although this may, in part, reflect a natural selection bias (i.e., patients who fail

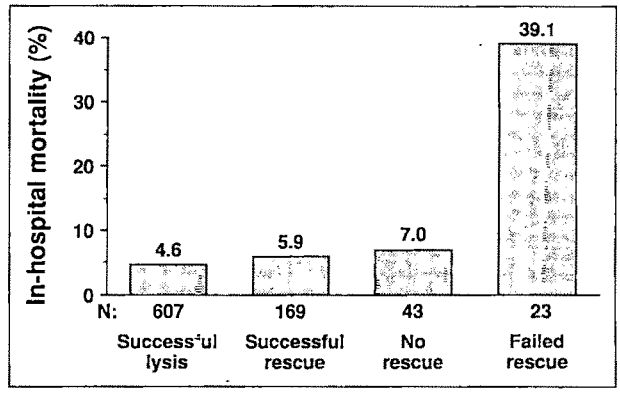


FIGURE 3. Impact of rescue percutaneous transluminal coronary angioplasty failure on in-hospital mortality. (Adapted from *J Am Coll Cardiol.*[32])

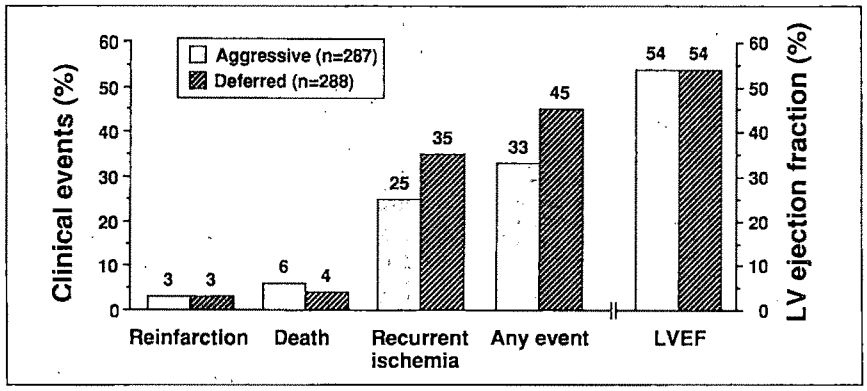


FIGURE 4. In-hospital outcomes of patients assigned to immediate cardiac catheterization (aggressive strategy) or predischarge catheterization (deferred strategy) in the TAMI-V study. LVEF = left ventricular ejection fraction. (Adapted from *Circulation*.[42])

pharmacologic thrombolysis may be inherently sicker and more hemodynamically compromised), it may also indicate that rescue angioplasty can precipitate hemodynamic and electrical instability. This latter explanation may be particularly true for rescue angioplasty of persistently occluded right coronary arteries, a procedure that appears to be associated with an increased risk of heart block and life-threatening ventricular arrhythmias.[32]

In addition to a retrospective analysis of the value of rescue angioplasty,[34] the TAMI study group has recently reported the results of a study that prospectively compared an aggressive interventional strategy with a more conservative post-thrombolytic strategy.[42] In TAMI-V, 575 patients were randomly assigned to undergo immediate coronary angiography with rescue angioplasty for failed thrombolysis, or predischarge cardiac catheterization after the administration of intravenous rt-PA, urokinase, or the combination of rt-PA and urokinase. The aggressive strategy was associated with a somewhat better predischarge regional infarct zone wall motion (−2.16 vs −2.49 standard deviations/chord, p = 0.004) and greater freedom from adverse clinical outcomes (67% vs 55%, p = 0.004) (Figures 4 and 5). In-hospital mortality was, however, slightly higher in the aggressively treated group (6% vs 4%), but this difference did not reach statistical significance.

The findings of these studies suggest that the role of rescue coronary angioplasty for failed pharmacologic therapy has not yet been defined adequately. Ongoing randomized trials will, it is hoped, further define the relative risks and benefits of this approach and may identify subgroups of patients in whom meaningful clinical benefits outweigh the potential hazards. Attention must also be given in future studies to the appropriate timing of mechanical revascularization in this setting. Conventionally, the angiographic success of pharmacologic thrombolysis has been recorded 90 minutes after initiation of the thrombolytic infusion. Thrombolysis continues beyond this point, however, and the patency rate may increase considerably between 90 minutes and 24–36 hours.[43] It is conceivable, therefore, that in some patients, PTCA of persistently occluded vessels could be deferred (to increase the likelihood of pharmacologic thrombolysis) without adversely affecting the extent of myocardial salvage or the likelihood of subsequent survival.

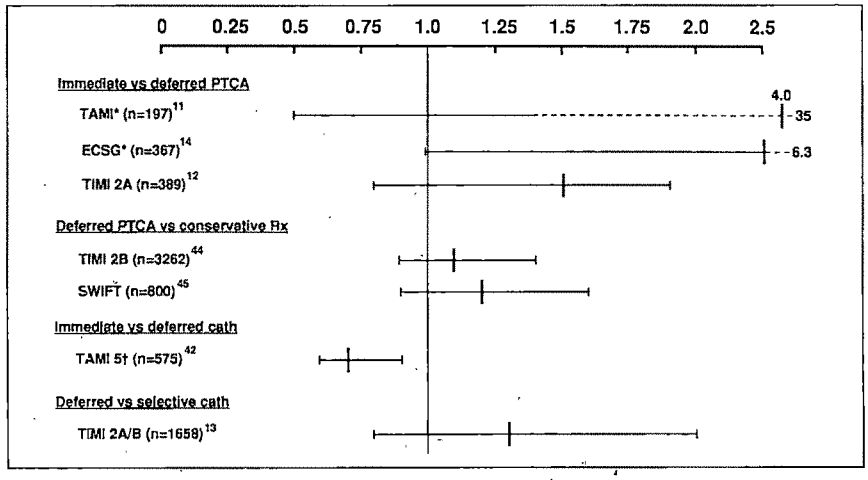


FIGURE 5. Impact of interventional strategy on clinical outcome at day 7 through 10 (TAMI, TAMI-V), day 21 (TIMI-IIA), day 42 (TIMI-IIB), day 90 (ECSG) and 1 year (SWIFT, TIMI-IIA/B). The vertical line indicates the relative risks of death or reinfarction of the more aggressive of the 2 strategies in each study. A relative risk < 1 indicates the treatment reduces the incidence of death or reinfarction; > 1 indicates an increased incidence of these outcomes. The horizontal line indicates the 95% confidence limits; superscript numbers indicate the reference number. PTCA = percutaneous transluminal coronary angioplasty; Rx = treatment; SWIFT=Should We Intervene Following Thrombolysis? trial. See Figure 1 for other abbreviations. *Incidence of death only; †any adverse event (death, stroke, reinfarction, recurrent ischemia or heart failure).

CONSERVATIVE POST-THROMBOLYTIC STRATEGY

The failure of immediate PTCA to improve the short- and long-term clinical outcome of patients treated with intravenous thrombolysis in 3 well-controlled studies raised questions about the need for mechanical intervention, and even routine diagnostic coronary angiography, at any time in the postinfarction period. A conservative, noninvasive strategy was, therefore, evaluated in 2 large, randomized trials.[44,45] After showing no advantage of immediate PTCA over deferred intervention, the TIMI study group compared a deferred PTCA strategy to a noninvasive strategy in a much larger population of patients.[44] Following the administration of intravenous rt-PA, 3,262 patients were randomly allocated to undergo either coronary angiography and balloon dilation of suitable infarct vessel stenoses 18–48 hours after admission, or to a conservative strategy. Patients in the latter group underwent diagnostic coronary angiography and mechanical revascularization only if myocardial ischemia recurred prior to hospital discharge, or if a predischarge functional study showed exercise-induced ischemia. Of the 1,636 patients assigned to the invasive strategy, 928 (56.7%) underwent attempted PTCA; 216 (13.2%) of the conservatively treated patients required PTCA within 14 days of admission for recurrent or provocable ischemia. The principal end points of the study were the incidence of reinfarction or death within 6 weeks of presentation. Secondary end points included rest and exercise left ventricular ejection fraction and exercise-induced myocardial ischemia. The study concluded that the conservative, clinically driven interventional strategy was associated with a clinical outcome that was at least as favorable as the more aggressive and invasive interventional strategy. The 2 groups were well matched with respect to age and sex distribution, time to treatment, and clinical condition at presentation. The early postinfarction survival was excellent in both groups, with a cumulative 6-week mortality of 5.2% in the invasive group compared with 4.7% in the conservatively treated group. Reinfarction occurred within the first 6 weeks in 5.9% and 5.4%, respectively (Figure 5). Similarly, no difference was apparent between the groups in resting left ventricular ejection fraction at hospital discharge (50.5% vs 49.9%, $p = 0.30$), or at 6 weeks (50.0% vs 50.4%, $p=0.51$) (Table II). There was, however, a greater stress-induced increase in ejection fraction in the invasive strategy group (3.3% vs 2.3%, $p = 0.02$) and a higher incidence of exercise-induced myocardial ischemia in the conservatively treated patients (17.7% vs 12.8%, $p < 0.001$).

The major conclusion of this study, that most patients can be successfully managed conservatively following thrombolysis, is supported by the findings of a European multicenter trial of delayed elective mechanical revascularization versus conservative therapy after intravenous anisoylated plasminogen activator complex therapy.[45] Patients who were pain free and hemodynamically stable during the first 24 hours of hospital admission were randomly assigned in the SWIFT (Should We Intervene Following Thrombolysis?) trial to one of 2 post-thrombolytic strategies. Patients assigned to the invasive strategy underwent diagnostic coronary angiography and, if appropriate, mechanical revascularization within 48 hours of randomization. Balloon dilation of persistently occluded vessels was not encouraged. As in the TIMI-IIB study, coronary angiography with mechanical revascularization was performed on patients assigned to the conventional care group only if they developed recurrent postinfarction angina or had stress-induced ischemia. Of the 397 patients assigned to early intervention, 377 (95%) underwent coronary angiography within 7 days of admission and 228 (57%) were revascularized (169 by balloon dilation and 59 by coronary artery bypass graft surgery). In contrast, angiography was performed for clinical indications in 54 (13%) of 403 patients treated conservatively. Of these, only 19 patients (4.7%) were revascularized during the initial hospital admission, and an additional 40 patients (10%) underwent revascularization procedures during the 12-month follow-up period. Despite the considerably greater frequency of intervention in the invasive group, no difference in infarct-free survival was apparent between the two groups. The cumulative 1-year mortality was 5.8% in the intervention group compared with 5.0% in the conservative care group ($p = 0.6$), and the incidences of reinfarction were 15.1% and 12.9%, respectively ($p = 0.4$) (Figure 5). Similarly, no differences were apparent in left ventricular functional recovery or symptom status at 12 months (Table II).

Although these data are very compelling, several factors may limit the interpretation of the findings of these 2 studies. First, in both studies, PTCA was performed 18–48 hours after intravenous thrombolysis in the invasive groups, a time that, although "deferred," is still early in the convalescent period. Although not formally tested in any of the randomized trials, it is possible that further deferral of the interventional procedure

until at least 1–2 weeks postinfarction might improve procedural outcome by allowing an adequate period for plaque stabilization and thrombus resolution. Angiographic studies have suggested, for example, that the morphology of the lesion in the infarct-related artery improves progressively over the 7–10 days after thrombolytic therapy, with resolution of intraluminal filling defects, a reduction in contour irregularity and a decrease in indices of lesion ulceration.[46] Thus, a truly deferred interventional strategy has not been tested against a noninvasive strategy. Secondly, although 67% of patients enrolled in the TIMI-IIB study were classified as "not-low-risk," the in-hospital and long-term mortality of patients treated conservatively in this study and in the SWIFT trial were low, suggesting that the patients enrolled may, in fact, have had an excellent prognosis, regardless of the interventional strategy. Thus, the ability of these studies to detect an important difference in outcomes may have been limited, and extrapolation of the results to higher risk patient subgroups, including the elderly and patients presenting more than 3–4 hours after symptom onset, should therefore be undertaken with some caution.

MANAGEMENT OF RECURRENT MYOCARDIAL ISCHEMIA

If a conservative post-thrombolytic strategy is adopted, what then is the optimal management of recurrent myocardial ischemia and hemodynamic compromise during the early convalescent period? The frequency with which urgent cardiac catheterization was performed for these complications during the initial hospitalization of conservatively treated patients has ranged from 12% in the TIMI-IIA study[12] to 26% in the TAMI-V study.[47] The rationale for aggressive intervention in this setting is that angiographic evaluation permits appropriate triage to urgent mechanical revascularization or to continued medical therapy. In nonrandomized studies, urgent coronary angioplasty has been shown to improve 30-day survival for patients with cardiogenic shock[48] and to treat acute ischemic mitral valve regurgitation successfully.[49] Staged balloon angioplasty has also been advocated for patients with multivessel coronary artery disease,[50] a group known to be at increased risk of postinfarction mortality.[51] Similarly, emergency coronary artery bypass surgery, performed for unsuccessful sequential intravenous rt-PA therapy and coronary angioplasty or for severe multivessel disease, has been shown to be a safe and effective therapy that, in one study, was associated with a substantial degree of improvement in both global and regional left ventricular function.[52]

This aggressive interventional approach for recurrent myocardial ischemia or hemodynamic instability was recently evaluated by the TAMI-V study group.[47] Of 288 patients initially allocated to a conservative treatment strategy, 54 (19%) underwent urgent cardiac catheterization within 24 hours and a further 21 patients (7%) required urgent intervention during the second to fourth hospital days. Coronary angiography showed that the infarct-related artery was occluded (TIMI flow grade 0 or 1) in 39%, but was patent in the remainder. Emergency coronary angioplasty was performed in 49% of the patients and 3% underwent emergency coronary artery bypass surgery. Despite this intervention, the need for urgent cardiac catheterization was associated with an increased in-hospital mortality (7% vs 3%, $p = 0.36$), and poorer predischarge left ventricular function (left ventricular ejection fraction 50 ± 11% vs 54 ± 11%, $p=0.12$). Multivariate analysis of 16 clinically available parameters identified only patient age and anterior wall myocardial infarction as independent predictors of the need for urgent intervention. The implications of this study are that recurrent ischemia and reinfarction, which are relatively common with currently available thrombolytic and anticoagulant regimens, are predicted poorly by clinical parameters. Further, these complications are associated with a significant morbidity and mortality despite aggressive interventional therapy. In the absence of a control group, it is unclear whether urgent intervention is the optimal treatment in this setting; it remains possible that some of these patients might respond better to repeated administration of intravenous thrombolytic therapy,[53] but this approach has not yet been adequately evaluated.

ROUTINE PREDISCHARGE DIAGNOSTIC CORONARY ANGIOGRAPHY

The final post-thrombolytic strategy that should be considered is routine predischarge coronary angiography without routine mechanical revascularization.[54] Using this approach, delineation of the coronary anatomy is performed primarily for prognostic purposes. The value of this approach has not been formally tested, but a nonrandomized comparison of selective and routine coronary angiography was performed by the TIMI study group using data acquired in the TIMI-IIA and -IIB studies.[55] The clinical outcomes of 197 patients assigned in the TIMI-IIA study to conservative management and

routine predischarge coronary angiography was compared with that of 1,461 patients assigned to selective cardiac catheterization (for recurrent or provocable ischemia) in the TIMI-IIB study. In the former group, coronary angiography was actually performed on 94% of the eligible patients compared with 35% of the patients in the selective catheterization group; 59.4% of the latter group had undergone invasive evaluation by the end of the 1-year follow-up period. The incidence of predischarge mechanical revascularization by coronary angioplasty or bypass graft surgery was similar in the 2 groups. At 1 year, the incidence of death and nonfatal reinfarction were similar in the 2 groups (Figure 5), but the number of hospital readmissions was greater in the selective coronary angiography group (37.9% vs 27.6%, p = 0.007). It could be concluded from this study that a reduction in the number of postinfarction angiographic procedures by 40% would substantially reduce health care costs and the risks to the patient of an unnecessary procedure. However, the added costs of routine angiography may well be offset by the 30% reduction in the need for hospital readmission and a reduction in the need for repeat (and perhaps even predischarge) exercise stress testing. Further, knowledge of the coronary anatomy may have a positive impact on the timing of hospital discharge,[56,57] the psychologic health, and the employability of patients with a good prognosis, such as those with minimal coronary disease[58] or disease confined to a side branch coronary artery. Finally, knowledge of the coronary anatomy may have an important influence on the selection of medical therapy for patients with uncomplicated infarcts. Recent data have suggested, for example, that long-term β blockade may reduce postinfarction mortality in patients with persistently occluded infarct-related arteries.[59]

CURRENT RECOMMENDATIONS

From the data given, several broad recommendations can be made for the use of adjuvant mechanical revascularization following intravenous thrombolysis. First, the majority of patients can be initially managed without urgent coronary angiography and PTCA. Patients with an uncomplicated course should undergo a submaximal stress test prior to hospital discharge and, in many cases, can be managed medically if the functional study shows no evidence of inducible myocardial ischemia. Our own bias is, however, that predischarge, diagnostic coronary angiography is a low risk, relatively inexpensive investigation that should be offered to virtually all patients. Certainly, patients with provocable myocardial ischemia should undergo coronary angiography, preferably before hospital discharge, and, depending on the coronary anatomy, should then undergo elective mechanical revascularization of diseased arterial segments. In centers with active cardiac catheterization laboratories, early coronary angiography (days 4 to 6) should be considered with a view to early patient discharge and return to work, particularly for young otherwise healthy patients without evidence of extensive myocardial infarction. In patients with evidence of a large, evolving myocardial infarction, persisting ischemic chest pain or hemodynamic instability at the time of admission, urgent coronary angiography remains a valuable diagnostic tool that permits triage to rescue PTCA for persistently occluded infarct vessels, urgent coronary artery bypass grafting for severe left main or triple vessel coronary disease or to medical therapy (and perhaps intra-aortic balloon pump support) if the infarct vessel is patent. This schema will undoubtedly require modification as data from ongoing clinical investigations become available and as more reliable noninvasive means are identified for determining peri- and postinfarction mortality risk for individual patients.

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Designing Thrombolytic Agents: Focus on Safety and Efficacy

Désiré Collen, MD, PhD

Thrombolytic therapy for evolving acute myocardial infarction (AMI) reduces infarct size, preserves ventricular function, and reduces mortality. Intravenous streptokinase is commonly followed by approximately 50% patency of coronary arteries within 90 minutes and by reduction of mortality by 25%. Recombinant tissue plasminogen activator (rt-PA) is more potent for coronary arterial thrombolysis, producing both more rapid and more frequent recanalization (approximately 75% patency at 90 minutes) with a dose of 100 mg given over 3 hours. Side effects (mainly bleeding) associated with the use of streptokinase and rt-PA are not markedly different. That the higher efficacy of rt-PA would translate into a larger reduction of mortality is suggested by the results of several small trials but remains to be confirmed in well-designed comparative clinical trials. This question has not been adequately answered by the recent International rt-PA/streptokinase mortality trial and the International Study on Infarct Survival (ISIS-3) study, because of concerns with respect to the role of conjunctive intravenous heparin administration and the dose of rt-PA used in ISIS-3. All available thrombolytic agents still have significant shortcomings, including the need for large doses to be maximally efficient, a limited fibrin specificity, and a significant associated bleeding tendency. New developments toward improved efficacy and fibrin-specificity of thrombolytic agents include the use of mutants of rt-PA, chimeric rt-PA or single chain urokinase plasminogen activator molecules, and antibody-targeted thrombolytic agents. Some of these artificial plasminogen activators have a 5- to 10-fold increased potency (thrombolytic activity per unit dose), but whether they are safe enough to be clinically useful remains to be established. The conjunctive use of anticoagulants and antiplatelet agents with thrombolytic agents increases their efficacy to an extent that monotherapy with a plasminogen activator alone is no longer tenable. Heparin and aspirin are only moderately efficient for acceleration of lysis and prevention of reocclusion, but are relatively safe. More selective thrombin inhibitors and antiplatelet agents are more potent, but their safety remains to be confirmed. Continued investigation in this area will provide new insights and promote progress toward the development of the ideal thrombolytic therapy, characterized by maximized stable coronary arterial thrombolysis with minimal bleeding.

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The beneficial effects of thrombolytic therapy for thromboembolic diseases are now well established and the side effects are in general less serious than was initially anticipated. This has resulted in a continuously expanding use of thrombolytic therapy, particularly in patients with evolving myocardial infarction. The limited efficacy and the occasional life-threatening side effects of current therapeutic schemes, however, remain a matter of concern and warrant further investigation into improved agents and strategies. Many aspects of the risk–benefit ratio of thrombolytic therapy are reviewed in the other articles in this supplement. Here, the focus is on safety and efficacy of thrombolytic strategies in terms of the dosing, duration, and nature of the thrombolytic agents used, the interactive effects of conjunctive antithrombotic agents, and the baseline characteristics of the patient. The available data from clinical trials will be reviewed and extrapolated to potential improvements with experimental agents or combinations. Although safety encompasses many adverse reactions, including arrhythmia and allergic reactions, this review will focus on bleeding side effects, and more particularly on intracerebral bleeding and ischemic stroke.

The present experience obtained in randomized clinical trials with thrombolytic therapy, in which at

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TABLE 1 Major Bleeding, Neurologic Events and Early Mortality in Large (> 500 Patients per Group) Controlled Clinical Trials with Intravenous Thrombolytic Agents

Study	Patient No.	Adjunctive Therapy		Major Bleeding (%)				Neurologic Events (%)					Early Mortality (%)				
		Aspirin	Heparin	Placebo	SK	t-PA	APSAC	Definition	Placebo	SK	t-PA	APSAC	End Point	Placebo	SK	t-PA	APSAC
ISAM[1]	Plac: 882	+	+	?	—	—	—	ICB	0	0	—	—	21 days	7.1	—	—	—
	SK: 859	+	+	—	?	—	—	ICB	—	0.5	—	—	21 days	—	6.3	—	—
GISSI-1[2]	Plac: 5852	?	?	?	—	—	—	(Stroke)	(0.9)	—	—	—	21 days	13.0	—	—	—
	SK: 5860	?	?	—	0.7	—	—	ICB (stroke)	—	0.2 (1.1)	—	—	21 days	—	10.7	—	—
ISIS-2[3]	Plac: 4238	–	?	0.2	—	—	—	ICB (stroke)	0.0 (0.9)	—	—	—	35 days	—	—	—	—
	SK: 8490	±	?	—	0.5	—	—	ICB (stroke)	—	0.1 (0.8)	—	—	35 days	—	—	—	—
	SK + ASA: 4239	+	?	—	0.5	—	—	ICB	—	0.1	—	—	35 days	—	—	—	—
ASSET[4]	Plac: 2493	–	+ (24 h)	—	0.4	—	—	ICB (stroke)	—	0.1 (1.0)	—	—	30 days	9.8	—	—	—
	Alt: 2512	–	+ (24 h)	—	—	1.4	—	ICB (stroke)	—	—	0.3 (1.1)	—	30 days	—	—	7.2	
AIMS[5]	Plac: 502	?	+	0.5	—	—	—	(Stroke)	(0.5)	—	—	—	30 days	12.2	—	—	—
	APSAC: 502	?	+	—	—	—	0.3	(Stroke)	—	—	—	(1.1)	30 days	—	—	—	6.4
TIMI-II[6]	Cons: 1626	+ (>24 h)	+	—	—	(4.2)*	—	ICB (stroke)		—	0.4 (0.8)	—	42 days	—	—	4.7	—
	Inv: 1636	+ (>24 h)	+	—	—	(4.6)*	—	ICB (stroke)	—	—	0.6 (1.4)	—	42 days	—	—	5.2	—
GISSI-2/International Study Group[7]	SK: 10,396	+	± (sc 12 h)	—	0.6	—	—	ICB (stroke)	—	0.3 (0.9)	—	—	Hospital (M 9 d)	—	8.5	—	—
	Alt: 10,372	+	± (sc 12 h)	—	—	0.9	—	ICB (stroke)	—	—	0.4 (1.3)	—	Hospital (M 9 d)	—	—	8.9	—
ISIS-3[8]	SK: 13,000	+	± (sc 4 h)	—	0.9	—	—	Prob.ICB (stroke)	—	0.3 (1.1)	—	—	35 days	—	10.5	—	—
	Dut: 13,000	+	± (sc 4 h)	—	—	0.9	—	Prob.ICB (stroke)	—	—	0.7 (1.5)	—	35 days	—	—	10.3	—
	APSAC: 13,000	+	± (sc 4 h)	—		—	1.0	Prob.ICB (stroke)	—	—	—	0.6 (1.5)	35 days	—	—	—	10.6

*Bleeding and hematologic event rates represent data obtained with 100 mg rt-PA in this highly invasive study.

AIMS = APSAC Intervention Mortality Study; Alt = alteplase; APSAC = anisoylated plasminogen-streptokinase activator complex; ASA = aspirin; ASSET = Anglo-Scandinavian Study of Early Thrombolysis; Cons = conservative approach; Dut = duteplase; GISSI-1 = Gruppo Italiano per lo Studio della Streptochinasi nell' Infarto Miocardico; GISSI-2 Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto Miocardico; ICB = intracranial bleeding; Inv = invasive approach; ISAM = Intravenous Streptokinase in Acute Myocardial Infarction; ISIS = International Study on Infarct Survival; Plac = placebo; Prob = probable; SK = streptokinase; TIMI = Thrombolysis in Myocardial Infarction; t-PA = alteplase or duteplase.

least 500 patients were allocated to each group, are summarized in Table I. In aggregate, the placebo-controlled studies have demonstrated that thrombolytic therapy with streptokinase,[1–3] recombinant tissue plasminogen activator (rt-PA)[4] or anisoylated plasminogen streptokinase activator complex (APSAC)[5] reduces mortality; and that the mortality benefit is achieved with acceptable frequencies of side effects. However, because of their simple design, these studies provide little or no information on the mechanisms by which clinical benefit is achieved.

The only 2 mega-trials performed to date that have compared the efficacy for mortality reduction of different thrombolytic agents in patients with acute myocardial infarction (AMI) have shown no difference in early mortality and, if anything, a higher intracerebral bleeding rate with the "high tech" rt-PA and APSAC than with the "low tech" streptokinase.[7,8] The argument could end here with the conclusion that more efficient thrombolytic agents do not confer better clinical outcome, but are associated with higher toxicity than the combination of streptokinase and aspirin, as was established by the Second International Study on Infarct Survival (ISIS-2). However, significant questions concerning the design and monitoring of the comparative mega-trials persist, which have been totally overlooked during the recent wide dissemination of the ISIS-3 results. It would, therefore, seem appropriate to analyze critically the available data before discussing potential further improvements of thrombolytic agents and strategies.

CURRENT STATUS OF THROMBOLYTIC THERAPY OF ACUTE MYOCARDIAL INFARCTION

The recognition that thrombosis within the infarct-related coronary artery plays a major role in the pathogenesis of AMI, and the observation that early administration of thrombolytic agents results in recanalization of occluded coronary arteries, have provided the basis for the development of thrombolytic therapy in AMI. The hypothesis underlying this form of treatment is that coronary artery occlusion leads to ischemia and cell death, resulting in ventricular dysfunction and reduced life expectancy, and that timely recanalization, within a time window that allows salvage of ischemic myocardium, reduces infarct size, preserves myocardial function, and reduces early and late mortality. The most rational treatment of patients with AMI is therefore likely to be thrombolytic therapy with agents or combinations that produce stable coronary artery recanalization as frequently and as rapidly as possible, but with acceptable safety. Late opening of an occluded coronary artery may have some beneficial effect by limiting left ventricular remodeling, improving the electrical stability of the heart, or providing collateral vessels to viable myocardium.[9] Further, adjunctive therapy with anticoagulant and/or antiplatelet agents clearly contributes to the efficacy of thrombolysis.

Comparative efficacy of streptokinase and rt-PA: Comparative studies between streptokinase and rt-PA have shown a difference in efficacy for early coronary artery recanalization[10]; this conclusion has been supported by results of several noncomparative studies with similar design and end points (for references, see Collen[11]). Coronary artery patency is present in approximately 22% of patients within 90 minutes after the start of placebo infusion (usually including heparin and occasionally aspirin), probably around 35% after 24–48 hours, and around 65% after 1–3 weeks. Streptokinase administration is associated with around 53% patency at 90 minutes and 75% after 1–3 weeks, whereas rt-PA, in combination with intravenous heparin, is associated with 75% patency at 90 minutes, 85% at 24–48 hours and 81% at 1–3 weeks.[12] This analysis may be somewhat biased in favor of placebo as a result of higher early mortality in placebo-treated patients than in patients given thrombolytic agents. It is, however, difficult to imagine from these data that late patency would be the primary determinant of clinical outcome. Early patency, measured around 90 minutes after the start of therapy, is significantly increased over placebo (22%) with either streptokinase (53%) or rt-PA (75%), whereas the efficacy for coronary recanalization with rt-PA is about 50% higher than with streptokinase.

Nevertheless, comparative studies between streptokinase and rt-PA have not shown a difference in preservation of left ventricular function,[13,14] in combined clinical outcome,[15] or in survival.[7,8] This lack of correlation between initial efficacy and clinical outcome may have several explanations. First, initial recanalization obviously needs to be sustained in order to convey benefit. In the absence of adequate anticoagulation, the higher initial efficacy of rt-PA indeed appears to be offset by more frequent reocclusion, as demonstrated in several recent trials with angiographic end points (Table II). Whereas heparin did not appear to affect patency at 90 minutes,[16] its omission markedly reduced the patency rates measured at 7–24 hours,[17] 48–72 hours (mean 55 hours)[18] or at 48–120

TABLE II Influence of Heparin on Coronary Patency Following Alteplase Infusion

		End point (Time after Start of Therapy)				
Heparin	Study	90 min	7–14 hr	48–72 hr	48–120 hr	Aspirin
With	Topol et al,[16] 1989	79% (50/63)				?
	Hsia et al,[17] 1990		82% (82/100)			No
	Bleich et al,[18] 1990			71% (30/42)		?
	ECSG,[15] 1991				83% (214/258)	Yes
Without	Topol et al,[16] 1989	79% (54/68)				?
	Hsia et al,[17] 1990		52% (43/93)			Yes
	Bleich et al,[18] 1989			43% (18/42)		?
	ECSG,[15] 1991				74% (181/244)	Yes
	p	0.83	<0.00_	0.015	0.022	

hours (mean 81 hours).[19] Similar studies with streptokinase are unfortunately not available, although some effect of heparin might also be inferred from the observed clinical benefit.[20] These data indicate that in order to obtain the high efficacy rates of rt-PA, concomitant use of intravenous heparin is required, whereas heparin's beneficial effect in association with streptokinase is less well documented. Consequently, the omission of immediate intravenous heparin in the International rt-PA/streptokinase mortality trial and in the ISIS-3 trial may well have accounted for the comparable clinical outcome. Second, if delayed recanalization were a major contributor to clinical benefit, the catch-up phenomenon observed with streptokinase within several hours might explain the comparable clinical outcome.[25] However, the hypothesis that delayed recanalization would be a major mechanism of salvage is invalidated by the finding, in many studies, that mortality reduction is highest in patients treated early. Third, there might be no direct correlation between recanalization and clinical benefit, but other (unknown) mechanisms might contribute. The main argument against this hypothesis is that early and sustained recanalization is the only mechanism with a demonstrated impact on myocardial necrosis. Fourth, the presently available mega-trials with clinical end points may have had flawed designs, precluding a demonstration of the potential differences in clinical benefit associated with differences in efficacy for coronary recanalization. A critical analysis of the 2 comparative mega-trials on thrombolytic therapy with streptokinase and rt-PA seems to support this hypothesis (see later). Additional arguments for and against early coronary recanalization as a major determinant of clinical outcome have been recently reviewed in detail.[12,21]

Issues resolved after the rt-PA/streptokinase mortality trial and the ISIS-3 study: The aim of the International rt-PA/streptokinase mortality trial[7] was to compare the efficacy and safety of 100 mg rt-PA (Activase, Genentech) given over 3 hours, with that of 1.5×10^6 U streptokinase given over 1 hour, in approximately 20,000 patients with AMI treated with aspirin and β blockade. In addition, the role of subcutaneous heparin, 12,500 U twice daily, started 12 hours after the onset of thrombolytic therapy, was evaluated. The primary end point, in-hospital mortality, was not significantly different between the streptokinase and rt-PA groups.[7] Although the aims and end points of the trial were simple and straightforward, the finding, during the course of the study, that the efficacy of rt-PA for coronary thrombolysis is strongly dependent on the conjunctive use of intravenous heparin has confused the issue.

The ISIS-3 study, reported at a press conference preceding the American College of Cardiology meeting in Atlanta in March 1991,[8] compared the effects of duteplase (Prolysis, Burroughs-Wellcome) 0.5×10^6 U/kg given over 4 hours, streptokinase 1.5×10^6 U over 1 hour, and APSAC 30 U given as a bolus. Approximately 45,000 patients with AMI entered the study and all were immediately treated with aspirin. In addition, the contribution of subcutaneous heparin, started 4 hours after thrombolytic therapy, was evaluated. The results indicated that early mortality was not significantly different with any of the thrombolytic agents, whereas the frequency of "probable" intracerebral hemorrhage was lower with streptokinase (0.3%) than with duteplase (0.7%) or APSAC (0.6%).

Irrespective of the problems associated with delayed subcutaneous heparin administration in ISIS-3, there are more serious questions concerning the dose of the duteplase preparation used. Indeed, because both Activase and Prolysis are the translation product of the same cDNA (obtained from mRNA of the Bowes melanoma cell line), they could be expected to have identical biologic properties. However, the production and/or purification processes appear to have introduced some artifacts in the Prolysis preparation, as suggested

by the specific activity, determined by clot lysis assays, which is markedly lower for Prolysis (approximately 300,000 IU/mg, based on data provided by Burroughs-Wellcome) than for Activase (580,000 IU/mg, based on data provided by Genentech) or for the melanoma t-PA standard (500,000 IU/mg as established by the International Committee for Thrombosis and Haemostasis). In contrast, kinetic chromogenic substrate assays yield a specific activity for duteplase of approximately 500,000 IU/mg, comparable to that of the standard melanoma t-PA. A dose of Prolysis of 0.6 *M* clot lysis U/kg body weight thus corresponds to 2 mg/kg body weight. For the average 75 kg patient, this would represent a total dose of 45×10^6 IU or 150 mg.

Extrapolation of the results obtained with duteplase in ISIS-3 to the standard use of 100 mg of rt-PA is not obvious. Indeed, based on the activity of both preparations, the 45×10^6 U dose of duteplase, given to the 75 kg patient in ISIS-3, would appear to be somewhat underdosed relative to the 58×10^6 U contained in 100 mg alteplase. Based on the gravimetric amount of material given in ISIS-3, however, the average dose of duteplase 150 mg clearly would be higher than alteplase 100 mg. Further, the Thrombolysis in Myocardial Infarction (TIMI-II) trial showed that alteplase 150 mg, given in combination with intravenous heparin, was associated with an intracerebral bleeding rate of 1.6%. This observation caused cessation of the testing of the 150 mg dose after several hundred patients and a reduction of the dose to 100 mg.

Equivalence between Prolysis and Activase in terms of efficacy for clot lysis in vivo has not been investigated in comparative studies in humans. However, each of the preparations has been compared with natural t-PA derived from the Bowes melanoma cell line in rabbits with experimental jugular vein thrombosis. On the one hand, we have established equivalence on a weight basis between Genentech's rt-PA and native t-PA, and, on the other hand, Emeis et al have established equivalence on a chromogenic assay activity basis between Wellcome's rt-PA and melanoma t-PA (Emeis J. J., personal communication). In view of these findings, which suggest thrombolytic equivalence of alteplase and duteplase on a weight basis, the intracerebral bleeding rate of 0.7% with duteplase 150 mg, given in combination with intravenous heparin, is not surprising.

This hypothesis of thrombolytic equivalence of alteplase and duteplase on a weight basis is fully supported by the frequency of intracranial bleeding in the International t-PA/streptokinase mortality study[7] and in ISIS-3[8] (Table III). Indeed, the frequency of cerebral bleeding as defined in these studies was identical, at 0.3%, in the streptokinase groups. The frequency of cerebral bleeding with 100 mg alteplase in the International t-PA/streptokinase mortality study was 0.4% (difference not significant), and with an average of 150 mg duteplase in ISIS-3 it was 0.7% ($p < 0.001$). The difference in cerebral bleeding rates between these studies thus appears to be primarily, if not totally, due to a difference between the 2 t-PA preparations (duteplase and alteplase) and not between alteplase and streptokinase. Thus, it appears that the claim that if physicians in the United States would switch from t-PA (alteplase) to streptokinase, there would be a difference of approximately 800 hemorrhagic strokes/year is without merit.

TABLE III Frequency of Cerebral Hemorrhage in the 2 Large Trials Comparing t-PA and SK in Patients with Acute Myocardial Infarction

	Definition	SK	t-PA	p
International Study/GISSI-2	Definite hemorrhage	30/10,396 (0.3%)	44/10,372 (0.4%)	NS
ISIS-3	"Probable" hemorrhage	39/12,848 (0.3%)	94/12,841 (0.7%)	<0.001
p		NS	0.003	

GISSI-2 = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; ISIS-3 = Third International Study on Infarct Survival; NS = difference not significant; SK = streptokinase; t-PA = tissue plasminogen activator.

Although the International rt-PA/streptokinase mortality trial and ISIS-3 have contributed significantly to the establishment of the safety of thrombolytic therapy with streptokinase, these studies cannot be heralded as the definitive tests of rt-PA versus streptokinase, nor as an indication that early and sustained recanalization does not primarily determine clinical outcome.

Is there a correlation between efficacy for early coronary recanalization and clinical outcome? The importance of the resolution of the present controversy on the cause/consequence relation between efficacy of coronary thrombolysis and clinical outcome for the future of thrombolytic therapy cannot be overstated. Indeed, if clinical benefit does not correlate with any quantifiable surrogate end point, evaluation of improvements would require mortality trials using a currently accepted regimen as control. Such trials, in order to obtain sufficient statistical power, would require several tens of thousands of patients. However, if clinical benefit does correlate with early and sustained recanalization of the occluded coronary artery, patency trials would constitute viable initial alternatives to mortality trials and the evaluation of several new developments in thrombolytic therapy

TABLE IV In-Hospital Mortality in Randomized Studies with rt-PA Versus SK, UK, or APSAC in Patients with Acute Myocardial Infarction*

Study	rt-PA	SK/UK/APSAC
ECSG-1[22]	3/64	3/65 (SK)
TIMI-I[23]	12/157	14/159 (SK)
White et al[13]	5/135	10/135 (SK)
PAIMS[14]	4/86	7/85 (SK)
TAMI-V[24]	8/191	15/190 (UK)
GAUS[25]	6/124	5/121 (UK)
TAPS[26]	5/218	17/217 (APSAC)
	43/975 (4.4%)	71/972 (7.3%)

*Heterogeneity index: chi-square = 4.76, p = 0.57; odds ratio rt-PA vs SK/UK/APSAC: 0.59 (95% CI: 0.41–0.37); p value of the difference: 0.0067.
APSAC = anisoylated plasminogen-streptokinase activato· complex; ECSG = European Cooperative Study Group; GAUS = German Activator Urokinase Study; PAIMS = Plasminogen Activator Italian Multicenter Study; rt PA = recombinant tissue plasminogen activator; SK = streptokinase; TAMI = Thrombolysis and Angioplasty in Acute Myocardial Infarction; TAPS = t-PA Versus APSAC Patency Study; TIMI = Thrombolysis in Myocardial Infarction; UK = urokinase.

would remain within reach. Then optimized therapeutic schemes could be developed, based on engineered plasminogen activators in combination with potent specific antiplatelet agents and/or anticoagulants, which would produce improved benefit–risk ratios at affordable cost (see later).

In the absence of conclusive studies with mortality end points, comparing streptokinase with rt-PA in the presence of conjunctive immediate intravenous heparin, it might be of interest to review in-hospital mortality data of smaller comparative trials with rt-PA in combination with heparin, against other nonfibrin-specific thrombolytic agents (streptokinase, urokinase, or APSAC) with presumed lower efficacy for coronary thrombolysis. The results of 7 trials performed to date are summarized in Table IV. Cumulative in-hospital mortalities were 43 of 975 (4.4%) patients randomly assigned to rt-PA and heparin, and 71 of 972 (7.3%) patients allocated to the non–fibrin-specific agent and heparin. Meta-analysis of the data yields an odds ratio for death with rt-PA versus the nonfibrin-specific agents of 0.59 (95% confidence interval: 0.41–0.87; p = 0.0067). It should be stressed that these results are derived from small studies that, although randomized, were not prospectively designed for mortality end points. However, they agree remarkably well with the values calculated on the basis of the hypothesis that the clinical outcome is primarily determined by the efficacy for coronary recanalization of the thrombolytic agent.

EFFICACY AND SAFETY OF CURRENT SCHEMES OF THROMBOLYTIC THERAPY IN ACUTE MYOCARDIAL INFARCTION

Effect of dose and duration of administration on efficacy and safety: The most widely used schemes for thrombolytic treatment of AMI consist of 1.5×10^6 U streptokinase given over 60 minutes, 100 mg rt-PA given over 3 hours, or 30 U APSAC given as a bolus. Although these treatments are given to thousands of patients each year, they have been selected on the basis of relatively limited dose-ranging studies using efficacy for coronary recanalization as an end point. These dose-ranging studies carried out with streptokinase,[27] rt-PA,[28] and APSAC[29] are reviewed elsewhere.

The standard dose of 1.5×10^6 U streptokinase over 60 minutes results in a coronary artery patency rate at 90 minutes of approximately 50%.[11] The relative safety and the clinical benefit of this treatment have been well demonstrated in the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI-1)[2] and ISIS-2 trials.[3] Although there is some indication that this dose may not be optimal,[27] it is unlikely that additional, more detailed dose-ranging studies will be performed or that this dose will be changed. Nevertheless, it should be realized that the standard use of streptokinase, in combination with aspirin and heparin, does not induce coronary artery recanalization within a time period useful for myocardial salvage in nearly half of the patients.

The standard scheme of 100 mg rt-PA, given over 3 hours, with conjunctive immediate intravenous heparin has mainly been established in the TIMI open phase trials.[28] Following initial patency studies with a 2-chain pilot phase preparation,[22,23] which suggested a high efficacy and very good safety for a dose of up to 1 mg/kg of 2-chain rt-PA over several hours, a dose of 150 mg of the primarily single-chain rt-PA, given over 6 hours, was initially selected.[28] The high initial infusion rate of 90 mg over 1 hour was selected to achieve a maximal early recanalization rate, although the patency rate at 90 minutes with a total dose of 100 mg (60 mg given over the first hour) was comparable. The protracted duration of the infusion was selected because of its apparent effect on reocclusion.[30] When it appeared that the 150 mg dose was associated with an increased cerebral bleeding rate, the dose was reduced to 100 mg,[31] producing a patency rate at 90 minutes of approximately 74%.[11] More recently, front-loaded infusion schemes of rt-PA, in which a 100 mg dose is administered over 90 minutes, have produced a patency rate in excess of 80%,[25,26] so far without an apparent increase in bleeding risk.

There are 3 potentially significant lessons to be learned from these dose-ranging studies with

alteplase: (1) Contrary to the initial impression, protracted administration of alteplase with conjunctive intravenous heparin does not appear to be required and may, in fact, potentiate bleeding; (2) the currently used dose of alteplase with conjunctive intravenous heparin has been selected for high initial efficacy and is associated with acceptable safety in patients under 70 years; and (3) the dose of rt-PA equivalent to 1.5×10^6 U streptokinase in terms of early coronary artery recanalization would be 35–50 mg given over 90 minutes.

An algorithm for the estimation of mortality reduction with thrombolytic therapy of acute myocardial infarction: Based on the assumption that early and persistent coronary artery recanalization is the primary mechanism of mortality reduction and on the observation that both failure to achieve early patency and reocclusion after initial recanalization are associated with a 2.5-fold higher mortality,[32] it is possible to construct an algorithm for the estimation of the effect of thrombolytic strategies on mortality. With M = overall mortality and m=mortality following early and persistent recanalization, the following estimations would apply:

1. In the absence of thrombolytic therapy, with an estimated early patency at 90 minutes of 20%[12] and negligible reocclusion: M = 0.20m + 0.80 (2.5m) = 2.20m.
2. Thrombolysis with streptokinase combined with aspirin, with an estimated early patency of 55% and a reocclusion rate of 5%[11,12]: M = 0.50m + 0.05 (2.5m) + 0.45 (2.5m) = 1.75m.
3. Thrombolysis with rt-PA in the absence of intravenous heparin, with an estimated 75% early patency and a reocclusion rate of 25%[16–19]: M = 0.50m + 0.25 (2.5m) + 0.25 (2.5m) = 1.75m.
4. Thrombolysis with alteplase and intravenous heparin, with an estimated 75% early patency and a reocclusion rate of 10%[11]: M = 0.65m + 0.10 (2.5m) + 0.25 (2.5m) = 1.53m.
5. Front-loaded rt-PA with intravenous heparin, with an estimated early patency rate of 86% and a reocclusion rate of 8%[26]: M = 0.78m + 0.08 (2.5m) + 0.14 (2.5m) = 1.33m.
6. Ideal thrombolysis with 100% early and persistent recanalization: M = 1.0m.

A few conclusions would follow from this exercise:

1. The maximal mortality reduction achievable with thrombolytic therapy of occluded coronary arteries would be (2.2−1.0)/2.2 = 0.55 or 55%.
2. The estimated mortality reduction with streptokinase and aspirin would be (2.2−1.75)/2.2 = 0.20; this estimate is in line with the results of the GISSI and ISIS trials.
3. The mortality with rt-PA in the GISSI-2/International Study and in ISIS-3 is in agreement with that predicted from the relative efficacy for coronary artery recanalization found in the Bleich et al,[18] Heparin-Aspirin Reperfusion Trial,[17] and European Cooperative Study Group (ECSG-6)[19] trials.
4. The expected mortality benefit of rt-PA with heparin (with an early recanalization rate of 75% and a reocclusion rate of 10%) versus streptokinase with aspirin (with an early patency rate of 55% and a reocclusion rate of 5%) would be (1.53 − 1.75)/2.2 = 0.1, or 10%.
5. If the patency results of the t-PA Versus APSAC Patency Study (TAPS) were confirmed in larger studies, the expected relative mortality reduction of front-loaded rt-PA over standard streptokinase would be (1.33 − 1.75)/2.2 = 0.19, or 19%.

Although this algorithm undoubtedly constitutes an oversimplification, and is amenable to refinement, it may be of some use to correlate the magnitude of differences in efficacy with that of differences in clinical outcome.

Should thrombolytic therapy with alteplase be tailored to the history and age of the patient? Present treatment with rt-PA is carried out with a standard dose of 100 mg, usually in combination with aspirin and intravenous heparin. The dose of rt-PA was initially set at 150 mg to obtain maximal early coronary artery recanalization, but had to be reduced because of excess intracranial bleeding,[31] and is presently set at 100 mg to be given over 1.5–3 hours. The use of intravenous heparin appears to be necessary to obtain maximal and persistent coronary recanalization.[17–19] Aspirin is usually given because it was shown in ISIS-2 to be beneficial by itself as well as in association with streptokinase. However, its beneficial effect on early recanalization with alteplase has not actually been demonstrated, whereas an interactive effect between aspirin and alteplase with respect to bleeding time prolongation and bleeding has been observed both in animal models[33,34] and in

patients.[35] It is at least theoretically possible that concomitant aspirin might be useful with the relatively ineffective streptokinase, resulting in approximately 50% early patency, whereas it might not add to the 75% early patency obtained with rt-PA. In this case, delayed administration of aspirin, such as performed in the TIMI-II trial,[6] would be preferable in order to prevent late reocclusion without initial potentiation of the bleeding tendency during alteplase infusion.

Whatever the optimal administration scheme of aspirin with rt-PA might be, in terms of serious bleeding side effects, it would appear that the aggressive use of potent thrombolytic agents (e.g., 100 mg rt-PA), with conjunctive aspirin and intravenous heparin, would confer maximal benefit in patients with large recent infarcts in which much myocardial salvage is possible. This was suggested by the very low early mortality (under 5% in patients <70 years) rates in the TIMI-II,[6] ECSG-5,[36] TAMI-V,[24] and TAPS[26] studies. In more evolved infarcts, or in some older patients, the advantages of aggressive recanalization may be more limited and/or partially neutralized by potential increased intracranial bleeding risks. In these cases, a less aggressive thrombolytic strategy with a reduced dose of a more potent agent (e.g., 50 mg rt-PA) or with a full dose of a less potent agent (e.g., 1.5×10^6 U streptokinase) might be preferable. Indeed, the equivalent doses of streptokinase and rt-PA for coronary artery recanalization at 90 minutes are 1.5×10^6 U over 60 minutes and 25–50 mg over 90 minutes, respectively. It would thus seem that a 50 mg dose of rt-PA, with immediate intravenous heparin, could be of comparable efficacy as streptokinase, but devoid of its hypotensive or allergic side effects.

The recent International rt-PA/streptokinase mortality trial and ISIS-3 trial have used a high dose of rt-PA (100 mg alteplase and 150 mg of duteplase respectively), with aspirin and delayed subcutaneous heparin in patients with AMI evolving up to 24 hours, and without age limit. Because early intravenous heparin is required for early and sustained recanalization with rt-PA, and because aspirin potentiates the effect of alteplase on bleeding, the potential clinical benefit of more rapid recanalization with rt-PA versus streptokinase could have been diluted (due to inadequate anticoagulation and inclusion of patients with negligible salvageable myocardium), whereas all patients were exposed to the increased bleeding risk of (very) aggressive thrombolysis, combined with premature use of aspirin.

APPROACHES TO IMPROVE THROMBOLYTIC THERAPY

Despite their widespread use, the currently available thrombolytic agents have a number of significant limitations (for references, see Collen[11,12]). Resistance to reperfusion within 90 minutes occurs in 25% of patients despite the use of the most potent thrombolytic agents or combinations. Stable coronary patency is not uniformly produced, and angiographically documented acute coronary reocclusion occurs in 5–25% of patients. The time to reperfusion is prolonged, with restoration of anterograde coronary flow requiring on average 45 minutes after initiation of therapy. Significant bleeding may occur, with a frequency of intracerebral bleeding of approximately 0.5%. rt-PA has a very short plasma half-life as a result of rapid hepatic clearance. Its therapeutic use probably requires continuous intravenous infusion, which is time consuming, expensive, and consumes a relatively large amount of material (50–100 mg). Therefore, the quest, on the one hand, for thrombolytic agents with a higher thrombolytic potency, specific thrombolytic activity, and a better fibrin-selectivity and, on the other hand, for thrombolytic strategies that overcome resistance to clot lysis, accelerate recanalization, prevent reocclusion, and reduce the bleeding tendency, remains open.

Several lines of research toward improvement of thrombolytic agents are presently being explored, including the construction of mutants and variants of rt-PA, chimeric (tissue and urokinase [u-PA]) plasminogen activators, and conjugates or chimeras of plasminogen activators and monoclonal antibodies. In addition, the optimal mode and dosing regimen of administration and the conjunctive use of antithrombotic (anticoagulant or antiplatelet) agents need to be explored further.

Engineered plasminogen activators: rt-PA mutants with deletion of the finger (F), epidermal growth factor (E), and first Kringle (K_1) domain have a significantly reduced plasma clearance. However, these molecules are frequently associated with a reduced specific thrombolytic activity, resulting in an unchanged or only marginally improved thrombolytic potency which is best demonstrated with bolus injection (for references, see Lijnen and Collen[37,38]). In aggregate, however, these studies suggest that domain deletion or substitution mutants of rt-PA do not constitute superior thrombolytic agents.

The t-PA of saliva from the vampire bat (*Desmodus rotundus*) is highly homologous with human t-PA but lacks the second Kringle domain and the

plasmin cleavage site for conversion to a 2-chain form. It was found to constitute a potent and fibrin-specific thrombolytic agent in rabbits with femoral arterial thrombosis.[39]

Mutations in residues 296–304 of t-PA confer resistance to plasminogen activator inhibitor-1 (PAI-1), with maintenance of the activity toward substrates.[40] In view of the large excess of t-PA over PAI-1 achieved during thrombolytic therapy, resistance of rt-PA mutants to PAI-1 may not constitute an obvious advantage over wild-type t-PA. Insofar as high PAI-1 levels may contribute to the occurrence of reocclusion, PAI-1 resistant mutants of t-PA may, however, be useful for maintenance infusion after initial thrombolysis.

The rationale for the construction of chimeras between t-PA and u-PA (scu-PA or tcu-PA) is based on 2 observations. First, the structures in t-PA responsible for its fibrin affinity are localized in the NH_2-terminal region. Second, the fibrin specificity of scu-PA is not dependent on the NH_2-terminal 143 amino acids, but is only preserved if the Lys^{158}-Ile^{159} peptide bond is intact. Chimeric proteins consisting of parts of the NH_2-terminal chain of t-PA and of the COOH-terminal region of scu-PA may, therefore, combine the mechanisms of fibrin selectivity of both molecules.

Several chimeric plasminogen activators consisting of various portions of t-PA and u-PA have been constructed and partially characterized (for references, see Collen et al[41]). Most authors have obtained chimeras that have maintained the enzymatic properties of u-PA or of t-PA, confirming that the catalytic domains of both enzymes are functionally autonomous. The fibrin affinity of these chimeras is, however, usually lower than that of wild-type t-PA. The thrombolytic properties and fibrin specificity of such chimeras were found to be very similar but not superior to those of scu-PA.[42] The combination of a partial fibrin affinity of t-PA with the enzymatic properties of scu-PA, thus, did not significantly improve the thrombolytic potency of the molecule. Surprisingly, a chimera consisting of the 2 Kringle domains of t-PA and the serine protease domain of scu-PA, which has little fibrin affinity in vitro,[43] but which has a 10-fold delayed in vivo clearance with relatively maintained specific thrombolytic activity, was found to have a markedly enhanced thrombolytic potency in venous and arterial thrombosis models in animals.[44]

Murine monoclonal antibodies conjugated to plasminogen activators may be utilized for targeting of the therapeutic agent to a thrombus. A thrombus contains both fibrin-rich and platelet-rich material, and targeting of plasminogen activators may thus be achieved via either antifibrin or antiplatelet monoclonal antibodies. Chemical conjugates of tcu-PA or scu-PA with monoclonal antibodies directed against the NH_2-terminal of the Bβ-chain of fibrin or against fragment D-dimer of human cross-linked fibrin (MA-15C5) were shown to have an enhanced fibrinolytic potency in vitro. The conjugates had a 5- to 10-fold higher thrombolytic potency and slower clearance than unconjugated scu-PA in experimental animal models of thrombolysis.[45,46]

Platelets may also be used as a target for plasminogen activators. Conjugates between antiplatelet monoclonal antibodies and plasminogen activators indeed have a significantly enhanced thrombolytic potency toward platelet-rich clots.[47,48]

The studies summarized herein indicate that several approaches have produced engineered plasminogen activators with an increased thrombolytic potency in experimental animal models. At the present time, it remains unknown whether these agents will be safe enough for clinical use in humans. Further, evidence is accumulating that the efficacy of thrombolysis can also be maximized with adequate conjunctive anticoagulant and/or antiplatelet strategies. If the high initial patency of 85% with front-loaded alteplase and conjunctive intravenous heparin[26] could be combined with effective strategies to prevent reocclusion, the potential additional benefit from engineered plasminogen activators might become relatively marginal. The potential advantage of the engineered thrombolytic agents would then consist of their ease of administration by bolus injection, a reduced total dose, and potentially an improved efficacy or safety profile.

Conjunctive antithrombotic therapy: The efficacy of both aspirin and heparin to accelerate coronary thrombolysis, to overcome resistance to lysis, and to prevent reocclusion seems to be limited. Even with the concomitant administration of heparin and aspirin, thrombolytic therapy does not produce maximal stable coronary artery recanalization in patients with evolving myocardial infarction (for references, see Collen[11,12]). This is not surprising in view of the unselective inhibition by aspirin of the synthesis of both proaggregatory and antiaggregatory prostaglandins, and of the relative inefficacy of heparin for the inhibition of clot-associated thrombin.[49–51]

Several alternative approaches to reduction of

platelet aggregation via pathways other than cyclooxygenase inhibition have recently been explored in animal models. These include the use of thromboxane synthase inhibitors, antagonists of the serotonin or endoperoxide receptors, and platelet glycoprotein IIb/IIIa (GPIIb/IIIa) receptor-blocking agents. The latter group includes monoclonal antibodies directed against the platelet GPIIb/IIIa receptor, arginine–glycine–aspartic acid (RGD)-containing peptides derived from viper venoms, and small synthetic RGD-containing peptides. Another potential approach for the prevention of platelet-rich coronary artery thrombosis and for the acceleration of clot lysis consists of the use of selective thrombin inhibitors, including hirudin and its derivatives, selective tripeptide chloromethyl ketones or synthetic thrombin inhibitors. Agents from each of these groups have been shown to be more effective than aspirin or heparin in preventing arterial thrombosis, in overcoming the resistance of platelet-rich thrombus to dispersion with thrombolytic agents, in accelerating arterial recanalization, and in reducing early and delayed reocclusion after reflow (for references, see Sobel[49] and Gold[51]). However, several if not all of these combinations produce a significant prolongation of the bleeding time, which may be indicative of an increased bleeding risk.

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Summary

Richard C. Becker, MD, and Joel M. Gore, MD

A scientific approach to problem solving, today as in the past, dictates from the outset that one or more well-defined questions be asked and distinct hypotheses be posed, which, using carefully designed and meticulously applied methods, may then be tested. The information obtained should be collected, processed, and analyzed with previously validated techniques, generating results that must be interpreted honestly and critically prior to dissemination throughout the scientific community. This fundamental exercise is vital to all forms of investigation, assuring continued advancement and the maintenance of scientific integrity.

During the past decade it has become clear that thrombolytic therapy is beneficial in selected patients with acute myocardial infarction (AMI). When examined closely, however, it is apparent that thrombolytic therapy is, in fact, in its infancy, as is our understanding of adjuvant strategies, including thrombin antagonists, platelet inhibitors, and mechanical intervention. Thus, it is crucial that the treatment of AMI in general, and thrombolytic therapy in particular, be viewed in the appropriate light, as distinct medical disciplines, and be developed on the basis of scientifically sound and mechanistically based facts and principles.

Intravenous administration of thrombolytic agents as a primary treatment for AMI is based on the premise that occlusive coronary arterial thrombosis, typically developing at the site of a ruptured atheromatous plaque, is the proximate cause of tissue necrosis. It has been established that a majority of intracoronary thrombi can be lysed with currently available agents and that early reperfusion limits the extent of myocardial damage. Large scale clinical trials have documented unequivocally that thrombolytic therapy improves in-hospital and long-term patient survival. Moreover, they have shown that the greatest overall benefit occurs in patients treated within several hours of symptom onset, suggesting that the mechanism of benefit is the prompt restoration of nutritive myocardial blood. Surprisingly, however, this fundamental hypothesis, which in essence represents the cornerstone of thrombolytic therapy, to date has not been tested adequately. As a result, the field now finds itself at a major evolutionary turning point. As succinctly outlined by Dr. Collen earlier in this supplement, unless the relation between early sustained patency—representing a readily testable surrogate end point—and clinical outcome can be established or disproved, the future of thrombolytic therapy may be limited to large, time-consuming and costly megatrials, using patient death as the primary end point. On the other hand, if the "fundamental" hypothesis can be proven, animal and human studies can proceed uninterrupted, establishing risk–benefit perspectives for current and future treatment strategies at an affordable cost. Lastly, it is our hope that clinicians and scientists devoted to the study of atherosclerotic coronary artery disease, AMI, and thrombolysis can focus on the mission at hand, casting aside differences, while sharing insights and ideas that ultimately will contribute to further scientific understanding and improved patient care.

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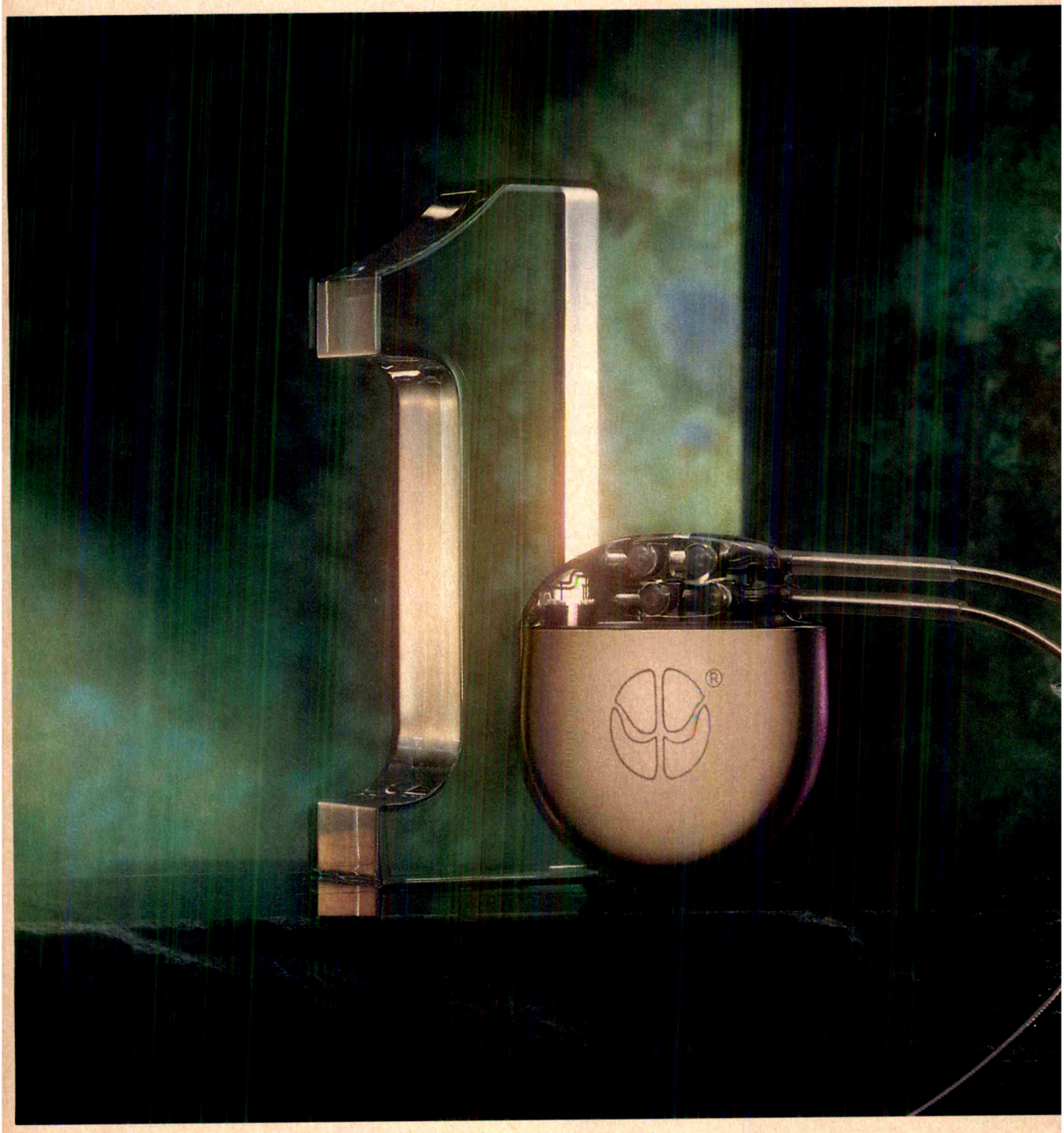
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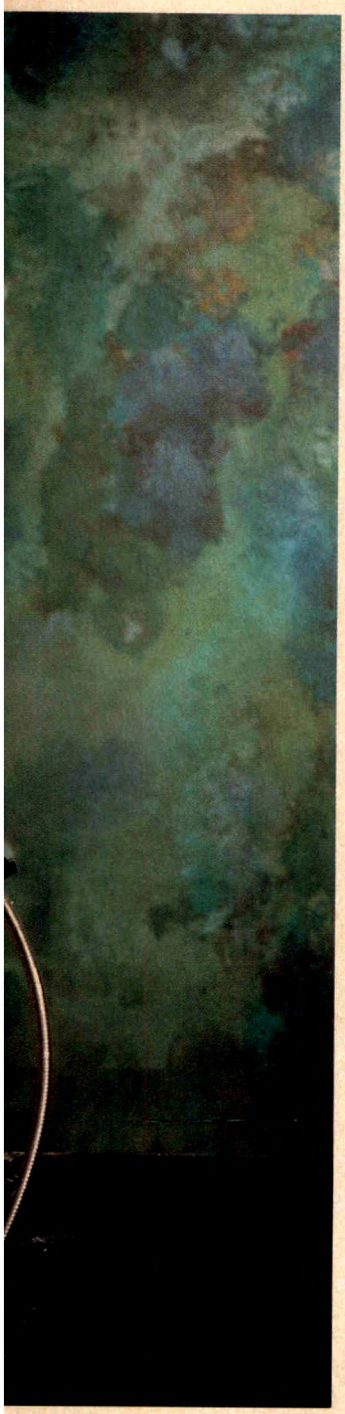
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*Pending FDA approval.

**Barbieri D, Percoco G, Toselli T et al. AV delay and exercise stres test: Behavior in normal subjects. PACE 1990; 13:1724-1727. See also Technical Manuals for all products listed.

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CORONARY ARTERY DISEASE

1

Assessment of Global and Regional Left Ventricular Performance at Rest and During Exercise After Thrombolytic Therapy for Acute Myocardial Infarction: Results of the Thrombolysis in Myocardial Infarction (TIMI) II Study

Barry L. Zaret, Frans J. Th. Wackers, Michael L. Terrin, Richard Ross, Melvin Weiss, James Slater, John Morrison, Robert C. Bourge, Eugene Passamani, Genell Knatterud, and Eugene Braunwald

Global and regional left ventricular (LV) performance were evaluated at rest and during exercise in patients who received recombinant tissue-type plasminogen activator therapy for acute myocardial infarction as part of the Thrombolysis in Myocardial Infarction II trial. Patients were randomized to either a conservative or invasive strategy and were evaluated at the time of hospital discharge and again at a 6-week follow-up with equilibrium radionuclide angiocardiography. Global and regional ejection fraction at rest were comparable in both treatment strategies. At the time of hospital discharge, patients in the invasive strategy had normal exercise responses more frequently, greater peak exercise LV ejection fraction, greater exercise — rest mean change in LV ejection fraction and greater peak exercise infarct zone regional ejection fraction than patients assigned to the conservative strategy. At 6-week follow-up, these differences between treatment strategies were no longer evident. This small transient difference in exercise global and regional LV performance associated with an invasive as opposed to conservative strategy is unlikely to confer clinical benefit.

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Influence of Collateral Filling of the Occluded Infarct-Related Coronary Artery on Prognosis After Acute Myocardial Infarction

James D. Boehrer, Richard A. Lange, John E. Willard, and L. David Hillis

This study was performed to assess the influence of collateral filling of an occluded infarct artery on long-term morbidity and mortality in surviving patients of initial myocardial infarction (AMI). Over 12.5 years, 146 patients with recent AMI, an occluded infarct artery and no other coronary disease were treated medically for 42 ± 28 months; 120 had collateral filling of the infarct artery, whereas the remaining 26 did not. The 2 groups were similar in age, sex, left ventricular function and infarct artery.

They were also similar in incidence of unstable angina, recurrent AMI, congestive heart failure and cardiac death. Thus, collateral filling of the infarct artery in surviving patients of AMI exerts no demonstrable effect on long-term morbidity or mortality.

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Predicting Arrhythmic Events After Acute Myocardial Infarction Using the Signal-Averaged Electrocardiogram

Jonathan S. Steinberg, Arlene Regan, Robert R. Sciacca, J. Thomas Bigger, Jr., and Joseph L. Fleiss, with the technical assistance of Donald E. Salvatore, Michael Fosina, and Linda M. Rolnitzky

To determine if the signal-averaged (SA) electrocardiogram (ECG) predicts the occurrence of sustained ventricular arrhythmia and sudden death after myocardial infarction, 182 consecutive patients with myocardial infarction underwent systematic noninvasive testing, including the SAECG. Seventy-one patients (39%) had an abnormal SAECG. There were 16 end points during 14-month follow-up. The SAECG was a significant predictor of these events ($p < 0.02$), and an abnormal SAECG conferred a 2.7-fold increase in risk, independent of both left ventricular function and ventricular arrhythmia on Holter ECG. When the results of the SAECG were combined with the results of the Holter ECG, a group of very high-risk patients was identified. Furthermore, all published studies with a similar design were pooled for meta-analysis that revealed a sixfold increase in risk, independent of left ventricular function, and an eightfold increase in risk, independent of Holter results when the SAECG was abnormal.

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Technetium-99m Sestamibi Myocardial Imaging at Rest for Assessment of Myocardial Infarction and First-Pass Ejection Fraction

Charles A. Boucher, Frans J. Th. Wackers, Barry L. Zaret, Ismael G. Mena, and the Multicenter Cardiolite Study Group

The ability of technetium (Tc)-99m sestamibi myocardial perfusion imaging at rest to evaluate myocardial infarction and first-pass ejection fraction was studied in a trial involving 18 institutions. Protocol I compared regional perfusion with occurrence of infarction by Q wave or by gated blood pool scan wall motion abnormality in 146 patients. Protocol II assessed first-pass right and left ventricular ejection fraction in 85 patients. In protocol I, Tc-99m sestamibi images were abnormal in 104 of 111 patients (94%) with both a Q wave and a gated scan wall motion abnormality and was normal in 23 of 25 patients (92%) in whom both were normal. Therefore, concordance existed in 105 (94%) patients. Of 115 patients with a Q wave, 107 (93%) had an abnormal Tc-99m sestamibi study. Of 115 patients with a gated scan wall motion abnormality, 108 (94%) had an abnormal Tc-99m sestamibi study. Of 17 myocardial segments per patient, there was concordance in 74% of patients. First pass Tc-99m sestamibi imaging of ejection fraction agreed well with conventional first-pass imaging for the right and left ventricle. Tc-99m sestamibi myocardial imaging at rest reliably diagnoses and localizes infarction and assesses ejection fraction by first-pass imaging.

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A Comparison Between Lovastatin and Gemfibrozil in the Treatment of Primary Hypercholesterolemia

Ralph B. D'Agostino, William B. Kannel, Miganush N. Stepanians, and LeiLanie C. D'Agostino

A randomized, multicenter, double-blind, prospective, 18-week comparison of lovastatin with gemfibrozil was performed to compare their efficacy and tolerability in adults with types IIa and IIb primary hypercholesterolemia. Each treatment group consisted of 52 patients. A total of 94 patients (90%) completed the 18 weeks of study. After 18 weeks of diet-plus-active treatment, lovastatin decreased serum total cholesterol and low-density lipoprotein (LDL) cholesterol significantly better than gemfibrozil. Gemfibrozil was more effective than lovastatin in increasing high-density lipoprotein (HDL) cholesterol and in decreasing very low density lipoprotein cholesterol and triglycerides. The 2 treatments were equally effective in reducing the total to HDL cholesterol ratio, but lovastatin was more effective in decreasing the LDL to HDL cholesterol ratio. Forty-nine percent of patients in the lovastatin group, and 9% of patients in the gemfibrozil group achieved goal LDL cholesterol levels ($p = 0.0001$). The 2 treatments were equally well tolerated.

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Blood Pressure, Plasma Atrial Natriuretic Peptide and Catecholamines During Rapid Ventricular Pacing and Effects of Beta-Adrenergic Blockade in Coronary Artery Disease

Keijo J. Peuhkurinen, Heikki V. Huikuri, Heikki Ruskoaho, and Juha T. Takkunen

Ventricular tachycardia was simulated by rapid ventricular pacing in 14 patients with coronary artery disease (CAD) and in 9 control subjects, and the effect of intravenous propranolol on blood pressure changes, plasma atrial natriuretic peptide (ANP) and catecholamine levels was evaluated. There was a rapid decrease in blood pressure after initiation of ventricular pacing, with subsequent recovery toward the end of the 2.5-minute pacing period. The pacing-induced increase in ANP was potentiated and blood pressure recovery blunted in both patient groups after β-adrenergic blockade. Pacing did not affect norepinephrine levels before propranolol, but after propranolol an increase was observed. The changes in blood pressure did not correlate with changes in ANP or norepinephrine, but the hormonal changes correlated with each other. Thus, hemodynamic recovery during simulated ventricular tachycardia is blunted after acute β-adrenergic blockade. Norepinephrine may have a specific role in counterbalancing the hypotensive action of ANP after β blockade, but the role of these hormones is less evident without β blockade. Although ANP and norepinephrine levels are correlated, blood pressure recovery must be determined also by other factors, such as neuroadrenergic system.

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Physiologic Responses to Recumbent Versus Upright Cycle Ergometry, and Implications for Exercise Prescription in Patients with Coronary Artery Disease

Scott C. Bonzheim, Barry A. Franklin, Christopher DeWitt, Charles Marks, Brian Goslin, Robert Jarski, and Sherry Dann

To clarify the influence of body position on exercise prescription, 14 men with coronary artery disease who underwent randomized recumbent and upright cycle ergometer tests to volitional fatigue were studied. Cardiorespiratory, hemodynamic and perceptual responses were compared at submaximal and maximal exercise. At a standard submaximal work rate (100 watts), heart rate (HR), systolic blood pressure, oxygen consumption ($\dot{V}O_2$) and rating of perceived exertion were greater in the upright than in the recumbent position. At peak exercise, however, these variables were not significantly different. Regressions of relative HR versus $\dot{V}O_2$ for recumbent and upright cycle ergometry were comparable. These findings indicate that recumbent exercise prescriptions may be based on the peak HR and $\dot{V}O_2$ values obtained during upright cycle ergometry, and vice versa. However, differences in the cardiorespiratory responses at submaximal exercise preclude the interchangeability of upright and recumbent training work rates.

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Prognostic Significance of Exercise Thallium-201 Testing in Patients Aged ≥70 Years with Known or Suspected Coronary Artery Disease

Thomas C. Hilton, Leslee J. Shaw, Bernard R. Chaitman, Karen S. Stocke, Henry M. Goodgold, and D. Douglas Miller

The prognostic value of exercise thallium-201 imaging in elderly patients (aged ≥70 years) was retrospectively examined in 120 patients referred for evaluation of coronary artery disease who underwent Bruce protocol exercise testing with quantitative planar thallium-201 scintigraphy. At mean follow-up of 36 ± 12 months there were 12 cardiac events (10%) (cardiac death or nonfatal myocardial infarction). The peak exercise stage (≤ or >Bruce stage I) and presence or absence of a thallium-201 defect risk-stratified the majority (64%) of elderly patients into very low- and high-risk subgroups with annual cardiac event rates of <1 and >15%, respectively.

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Feasibility of High-Dose Dipyridamole-Magnetic Resonance Imaging for Detection of Coronary Artery Disease and Comparison with Coronary Angiography

Frank M. Baer, Kamilla Smolarz, Markus Jungehülsing, Peter Theissen, Udo Sechtem, Harald Schicha, and Hans H. Hilger

To assess the feasibility of gradient-echo magnetic resonance imaging (MRI) for the detection of coronary artery disease (CAD), 23 patients with severe CAD underwent MRI of corresponding short-axis tomograms at rest and after dipyridamole infusion, and additionally performed a conventional exercise stress test. All tomograms were graded as normal,

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hypokinetic, akinetic or dyskinetic on a standardized segmental basis. Dipyridamole-MRI was considered pathologic if new wall motion abnormalities of ≥1 grade occurred. The location of segments with dipyridamole-induced wall motion abnormalities was compared with coronary angiography findings. Dipyridamole-MRI was pathologic in 78%, and exercise stress testing in 66% of all patients. Sensitivity of dipyridamole-MRI for the localization of stenosed coronary arteries was 78, 73 and 88% for left anterior descending, left circumflex and right coronary arteries, respectively. It is concluded that dipyridamole-MRI is a feasible nonexercise-dependent test for the detection and localization of functionally significant CAD.

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Intracoronary Urokinase as an Adjunct to Percutaneous Transluminal Coronary Angioplasty in Patients with Complex Coronary Narrowings or Angioplasty-Induced Complications

Evelyne Goudreau, Germano DiSciascio, George W. Vetrovec, Youssef Chami, Ravinder Kohli, Mark Warner, Nagui Sabri, and Michael J. Cowley

The effectiveness of intracoronary urokinase as an adjunct to coronary angioplasty was studied in 50 patients who had complex coronary narrowings or thromboembolic complications during percutaneous transluminal coronary angioplasty (29 [58%] men, 37 [74%] unstable angina, and 16 [32%] prior bypass surgery). Urokinase was infused at 5,000 to 20,000 IU/min; mean (± standard deviation) dosage was 399,000 ± 194,000 IU. Angiographic success was achieved in 43 patients (86%). Complications included the need for urgent bypass surgery in 3 patients, and myocardial infarctions in 14 (12 non-Q wave). Two patients died (1 of causes unrelated to the procedure). Fibrinogen levels were 355 ± 73 mg/dl before and 361 ± 70 after urokinase infusion. It is concluded that intracoronary urokinase is an effective adjunct to coronary angioplasty of narrowings with associated thrombi and may improve the success rate in angioplasty complicated by thrombus formation.

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Peripheral Vascular Complications After Conventional and Complex Percutaneous Coronary Interventional Procedures

David W. M. Muller, Kenath J. Shamir, Stephen G. Ellis, and Eric J. Topol

Peripheral vascular complications were identified in 35 patients after 39 of 2,400 consecutive cardiac catheterization procedures (1.6%). The incidence after 1,519 diagnostic studies was 0.6%, after 698 conventional coronary balloon angioplasties 2.6% and after 183 complex interventional procedures 6.0% ($p < 0.0001$). By univariate analysis, variables predicting the likelihood of vascular complications included: periprocedural use of heparin ($p < 0.001$) or fibrinolytic therapy ($p < 0.001$), arterial sheath size ≥8Fr ($p < 0.001$), patient age ≥65 years ($p = 0.01$) and peripheral vascular disease ($p = 0.03$). These data suggest that the increased incidence of access site complications after complex interventional procedures is likely to be related predominantly to procedural factors and, in particular, to the need for large caliber arterial sheaths, and the use of adjunctive anticoagulant or thrombolytic therapy.

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Results of Coronary Angioplasty of Chronic Total Occlusions (the National Heart, Lung, and Blood Institute 1985–1986 Percutaneous Transluminal Angioplasty Registry)

Nicholas A. Ruocco, Jr., Michael E. Ring, Richard Holubkov, Alice K. Jacobs, Katherine M. Detre, David P. Faxon, and the Co-Investigators of the National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry

The acute and long-term outcome in 271 patients after angioplasty (142 single and 129 multilesion) of a total occlusion was compared with 1,429 patients undergoing angioplasty of a subtotal occlusion (885 single and 544 multilesion). Acute success was lower ($p < 0.001$) in the patients with total occlusion for both single (61 vs 86%) and multilesion (57 vs 76%) angioplasty. Major complications (death, myocardial infarction or emergency bypass surgery) were similar between patients with total and subtotal occlusions for single (6 vs 7%) and multilesion angioplasty (9 vs 6%). At 2 years, mortality was significantly higher in patients with total occlusion. There were no differences between the 2 groups in cumulative event rates for myocardial infarction or bypass surgery. Approximately three-fourths of patients in each group were free of angina at 2 years. Acute and long-term success (angina improved and free of a major complication) for angioplasty of a single total occlusion was predicted by 1-vessel disease and estimated occlusion duration of <2 months.

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Establishing Comprehensive, Quantitative Criteria for Detection of Restenosis and Remodeling After Percutaneous Transluminal Coronary Angioplasty

Nicoletta B. de Cesare, Paula R. Williamson, Noel B. Moore, Scott F. DeBoe, and G. B. John Mancini

To establish quantitative and comprehensive criteria for detecting restenosis and remodeling after interventions, inter- and intraobserver variability of 2 observers were tested using quantitative arteriography software in the analysis of 20 lesions immediately after percutaneous transluminal coronary angioplasty (PTCA) and after a follow-up of 6 months. Observers were given only the location of the lesion, whereas frame selection and details of digitization were left up to the discretion of the individual observers. We showed a high inter- and intraobserver reproducibility of the absolute geometric parameters. Biplane percent area stenosis was also highly reproducible and there were no major differences between the analysis of post-PTCA and follow-up lesions. On the other hand, single-plane percent densitometric area stenosis measurements were highly variable. This variability decreased when densitometric measurements in orthogonal views were averaged. Therefore, geometric measurements are well suited for quantitative analyses. Despite its theorectical attraction, this analysis does not support the use of videodensitometry in evaluating PTCA results.

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Comparison of Ischemic and Physiologic Responses During Exercise Tests in Men Using the Standard and Modified Bruce Protocols
Kyle J. McInnis, Gary J. Balady, Donald A. Weiner, and Thomas J. Ryan

Thirty-two patients with documented stable coronary artery disease performed symptom-limited exercise tests using the standard and modified Bruce protocols in a random order, 1 hour apart, to determine the effects on the ischemic threshold. Patients achieved higher peak heart rate, rate-pressure product and oxygen consumption (VO_2) using the more abrupt standard Bruce protocol, but there were no differences in these parameters at matched submaximal work rates. Time to ischemic ST changes was significantly longer using the modified Bruce protocol, but heart rate, rate-pressure product, VO_2, and systolic and diastolic blood pressures were not different at ischemic ST depression. These data indicate that peak values of myocardial oxygen demand and total body VO_2 are higher during the standard Bruce protocol, but the ischemic threshold is similar during tests on these 2 frequently used protocols.

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Comparison Between Technetium-99m–Teboroxime and Thallium-201 Dipyridamole Planar Myocardial Perfusion Imaging in Detection of Coronary Artery Disease
Chantal Labonté, Raymond Taillefer, Raymond Lambert, Fadi Basile, Tuan TonThat, Michel Jarry, and Jean Léveillé

The purpose of this prospective study was to compare technetium-99m (Tc-99m)–teboroxime to thallium-201 imaging after the administration of dipyridamole. Thirty patients referred for the evaluation of chest pain were studied with both thallium-201 and Tc-99m–teboroxime dipyridamole scans (mean interval 2 days). Planar imaging was obtained at 5 and 240 minutes after the injection of 2.2 mCi of thallium-201. Tc-99m–teboroxime (18 to 25 mCi) was injected after dipyridamole infusion. A second injection, at rest, was repeated 4 hours later. Planar imaging was obtained 2 minutes after the Tc-99m–teboroxime injection. Thallium-201 detected perfusion defects in 182 myocardial segments corresponding to 33 of 45 (73%) significantly stenosed coronary arteries, and Tc-99m–teboroxime detected 160 abnormal segments corresponding to 29 of 45 (64%) stenosed arteries. In conclusion, this study shows that there is a good correlation in the imaging results found with thallium-201 and Tc-99m–teboroxime using dipyridamole infusion on both a segmental and a diagnostic comparison.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

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Exercise Testing and Thallium-201 Emission Computed Tomography in Patients with Intraventricular Conduction Disturbances

Kei Tawarahara, Chinori Kurata, Takahisa Taguchi, Akira Kobayashi, and Noboru Yamazaki

The specificity of exercise thallium-201 emission computed tomography for detecting coronary artery disease was assessed in patients with intraventricular conduction disturbance. Eighty-seven patients were studied: 33 with right bundle branch block (RBBB), 11 with RBBB and abnormal left-axis deviation, 11 with left (L)BBB, 12 on right ventricular pacing (RV pacing) and 20 with Wolff-Parkinson-White (WPW) syndrome. Specificity in patients with LBBB (30%), right ventricular pacing (44%) or RBBB plus left-axis deviation (50%) was significantly lower than in 349 control patients with normal intraventricular conduction (94%; $p < 0.01$). There was no significant difference between patients with RBBB (86%) or WPW syndrome (90%). Furthermore, diffuse slow washout was frequently noted in patients with WPW syndrome (35%) compared with those with normal intraventricular conduction (11%; $p < 0.05$). This study suggests that the incidence of perfusion and clearance abnormalities during exercise thallium-201 emission computed tomography is high in patients with intraventricular conduction disturbance.

CONGESTIVE HEART FAILURE

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Effects of Enalapril on Long-Term Mortality in Severe Congestive Heart Failure

John Kjekshus, Karl Swedberg, and Steve Snapinn, for the CONSENSUS Trial Group

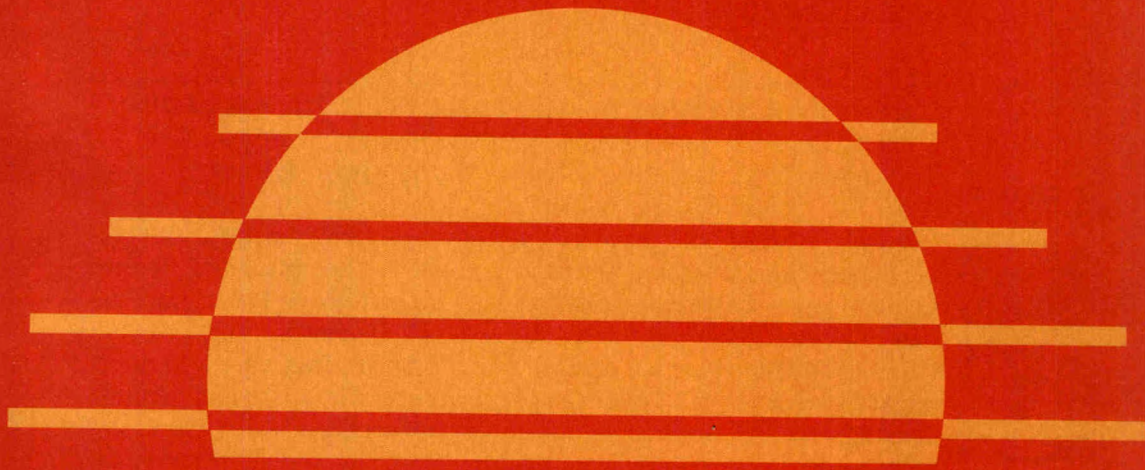
All surviving patients in a double-blind study comparing the effects of enalapril and placebo on survival in severe congestive heart failure were recommended to be treated with active drug after stopping the trial. Two-year follow-up from the end of the blinded trial demonstrated that among 77 survivors of 127 patients originally allocated to the group with enalapril, 38 were still alive. Of 126 patients allocated to the group with placebo 58 survived the blinded study, and after 2-year follow-up 26 were still alive. Thus, the difference between the original treatment groups remained, despite that treatment with enalapril was made available to all surviving patients and that those in the group with enalapril were sicker at baseline than those in the group with placebo. If enalapril was prescribed, the mortality was 47% compared with 75% if it was not. This strongly suggests that enalapril confers long-lasting protection to the failing myocardium.

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VALVULAR HEART DISEASE

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Left Ventricular Filling and Ventricular Diastolic Performance After Percutaneous Balloon Mitral Valvotomy

J. Kevin Harrison, Charles J. Davidson, James B. Hermiller, Michael B. Harding, J. Douglass Hanemann, Jack T. Cusma, Katherine B. Kisslo, and Thomas M. Bashore

Left ventricular (LV) filling and LV diastolic function were studied in 27 patients before and acutely after balloon mitral valvotomy (BMV). Simultaneous pressure-volume data were obtained using digital subtraction left ventriculography and LV micromanometer pressure. The mitral valve area increased from 1.1 ± 0.3 to 2.1 ± 0.8 cm^2 and the left atrial pressure decreased from 22 ± 5 to 14 ± 5 mm Hg after BMV. The time constant of LV isovolumic relaxation was unchanged after BMV; 50 ± 10 vs 47 ± 13 ms. In addition, LV end-diastolic volume, end-diastolic pressure and diastolic filling time were not altered by BMV. The percentage of filling in the first third of diastole was similar before and after the procedure, although there was a trend toward earlier occurence of the peak filling rate. Thus, the time course of LV filling is not significantly altered acutely after BMV, but is maintained at reduced left atrial pressure. Neither LV relaxation or LV chamber compliance are altered after BMV. These data suggest that the decreased correlation between invasive and Doppler data obtained acutely after BMV is not due to changes in LV diastolic function. In addition, the lack of impairment of LV isovolumic relaxation suggests that LV ischemia or papillary muscle injury is unlikely to contribute to increased mitral regurgitation after BMV.

MISCELLANEOUS

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Cardiac Function After Domino-Donor Heart Transplantation

Catherine M. Kells, Sara Marshall, Mordecai Kramer, Sharon A. Hunt, James Theodore, Hannah A. Valantine, and Vaughn A. Starnes

Cardiac transplantation using the explanted heart from a patient undergoing heart-lung transplantation was examined. This procedure, termed domino-donor heart transplantation, was successfully performed in 7 patients who are all alive at a mean follow-up of 20 months (range 1 to 26). Right ventricular function and morphology have either improved or remained unchanged in all patients. The incidence of infection and rejection is similar to that of patients undergoing conventional heart transplant procedures. These data indicate that domino-donor cardiac transplantation is an appropriate means of augmenting the donor pool.

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Predictive Factors of Effectiveness of Streptokinase in Deep Venous Thrombosis

Claude Théry, Jean Jacques Bauchart, Martine Lesenne, Philippe Asseman, Jean-Gabriel Flajollet, Raphaël Legghe, and Philippe Marache

In a prospective study, 174 patients with deep venous proximal extensive thrombosis received streptokinase through the catheter of a temporary vena caval filter. In cases where the thrombus was not occlusive, 60% of patients were discharged with a normal venogram versus 14% of those with occlusive clots. Among nonocclusive clots, those that are proximal are more easily lysed. In 31% of patients, a clot appeared in the filter. Clinical follow-up was performed in 70 patients at an average of 34 months. When venographic results showed no clots at discharge, 86% of patients were free of clinical sequelae versus 33% of those without normal phlebograms. It is concluded that: (1) in the case of occlusive clots, only a few patients were normalized after streptokinase; (2) proximal nonocclusive clots are most effectively lysed; (3) when venograms were free of clots at discharge, the majority of patients did not have venous sequelae at follow-up; and (4) embolic migration seems to occur frequently with streptokinase.

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Cardiovascular Factors Influencing Survival in End-Stage Renal Disease Treated by Continuous Ambulatory Peritoneal Dialysis

Jürgen Hüting and Georg Schütterle

To identify cardiac risk factors for increased mortality in end-stage renal disease, 55 patients on continuous ambulatory peritoneal dialysis (CAPD) were followed up for >35 months in a prospective noninvasive analysis. Risk factors of 25 nonsurvivors compared with 30 survivors were older age, angina pectoris, moderate left ventricular systolic and severe left ventricular diastolic dysfunction as seen on echocardiography and Doppler echocardiography; duration of CAPD or parameters of blood chemistry were not risk factors. The findings may be useful for identifying CAPD patients with high mortality risk and to direct therapeutic efforts.

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Left Ventricular Function in Myasthenia Gravis

Karl-Arne Johannessen, Åse Mygland, Nils Erik Gilhus, Johan Aarli, and Harald Vik-Mo

Left ventricular diastolic filling was studied in 25 patients with myasthenia gravis and in 25 control subjects by Doppler echocardiography. M-mode peak filling rate was 37% lower, and diastolic mitral peak early filling velocity (E) was 12% lower, whereas peak atrial filling velocity (A) was 38% higher in the patients with myasthenia, resulting in a 33% lower E:A ratio. Systolic measures were normal. Intake of the acetylcholine-esterase inhibiting drug pyridostigmine resulted in a normalization of the diastolic measures in the patients with myasthenia. Peak filling rate increased by 23%, E increased by 9%, A decreased by 9%, and the E:A ratio increased by 16%. Diastolic measures in the control subjects did not change after pyridostigmine. These findings document significant alter-

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*In hypertension, CAPOTEN may be used as initial therapy (25 mg bid or tid) for patients with normal renal function, in whom the risk of neutropenia/agranulocytosis is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for hypertensives who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations.

†In heart failure, CAPOTEN should generally be added to diuretics and digitalis except when digitalis use is poorly tolerated or otherwise not feasible; add CAPOTEN when patients have not responded adequately.

CAPOTEN is contraindicated in patients who are hypersensitive to this product. Angioedema has been reported in patients receiving ACE inhibitors.

Please see INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary on the adjacent page.

ations of diastolic filling in some patients with myasthenia gravis, and that the acetylcholine-esterase inhibiting drug pyridostigmine tends to normalize diastolic filling in these patients.

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F SUMMARY

ATIONS AND USAGE: LOZOL (indapamide) is indicated for the treatment of tension, alone or in combination with other antihypertensive drugs, and for the ment of salt and fluid retention associated with congestive heart failure.
e in Pregnancy: See PRECAUTIONS.

TRAINDICATIONS: Anuria, hypersensitivity to indapamide or other sulfonamide-ed drugs.

NINGS: Infrequent cases of severe hyponatremia, accompanied by hypokalemia, been reported with the use of recommended doses of indapamide primarily in y females. Symptoms were reversed by electrolyte replenishment (see AUTIONS). Hypokalemia occurs commonly with diuretics (see ADVERSE TIONS, hypokalemia), and electrolyte monitoring is essential. In general, diuretics d not be given with lithium.

AUTIONS: Perform serum electrolyte determinations at appropriate intervals, ially in patients who are vomiting excessively or receiving parenteral fluids, in nts subject to electrolyte imbalance, or in patients on a salt-restricted diet. In on, patients should be observed for clinical signs of fluid or electrolyte imbalance, as hyponatremia, hypochloremic alkalosis, or hypokalemia. The risk of kalemia secondary to diuresis and natriuresis is increased with larger doses, with diuresis, with severe cirrhosis, and with concomitant use of corticosteroids or . Interference with adequate oral intake of electrolytes will also contribute to kalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the effects of digitalis, such as increased ventricular irritability.
onal hyponatremia may occur in edematous patients; appropriate treatment is ly water restriction. In actual salt depletion, appropriate replacement is the ment of choice. Chloride deficit is usually mild, not requiring specific treatment t in extraordinary circumstances (liver, renal disease).
uricemia may occur, and frank gout may be precipitated in certain patients ving indapamide. Serum concentrations of uric acid should be monitored dically.
with caution in patients with severe renal disease; consider withholding or ntinuing if progressive renal impairment is observed. Renal function tests should erformed periodically.

Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. Latent diabetes may become manifest and insulin requirements in diabetic patients may be altered during thiazide administration. Serum concentrations of glucose should be monitored routinely during treatment with indapamide.
Calcium excretion is decreased by diuretics pharmacologically related to indapamide. Serum concentrations of calcium increased only slightly with indapamide in long-term studies of hypertensive patients. Indapamide may decrease serum PBI levels without signs of thyroid disturbance. Complications of hyperparathyroidism have not been seen. Discontinue before tests of parathyroid function are performed.
Thiazides have exacerbated or activated systemic lupus erythematosus. Consider this possibility with indapamide.

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In mouse and rat lifetime carcinogenicity studies, there were no significant differences in the incidence of tumors between the indapamide-treated animals and the control groups.

Pregnancy Category B: Diuretics cross the placental barrier and appear in cord blood. Indapamide should be used during pregnancy only if clearly needed. Use may be associated with fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse effects that have occurred in adults. It is not known whether this drug is excreted in human milk. If use of this drug is deemed essential, the patient should stop nursing.

ADVERSE REACTIONS: Most adverse effects have been mild and transient. From Phase II placebo-controlled studies and long-term controlled clinical studies, adverse reactions with ≥ 5% cumulative incidence: headache, dizziness, fatigue, weakness, loss of energy, lethargy, tiredness or malaise, muscle cramps or spasm or numbness of the extremities, nervousness, tension, anxiety, irritability or agitation; < 5% cumulative incidence: lightheadedness, drowsiness, vertigo, insomnia, depression, blurred vision, constipation, nausea, vomiting, diarrhea, gastric irritation, abdominal pain or cramps, anorexia, orthostatic hypotension, premature ventricular contractions, irregular heart beat, palpitations, frequency of urination, nocturia, polyuria, rash, hives, pruritus, vasculitis, impotence or reduced libido, rhinorrhea, flushing, hyperuricemia, hyperglycemia, hyponatremia, hypochloremia, increase in serum BUN or creatinine, glycosuria, weight loss, dry mouth, tingling of extremities. Clinical hypokalemia occurred in 3% and 7% of patients given indapamide 2.5 mg and 5.0 mg, respectively. In a long-term study (157 patients) potassium supplementation was given to 12% and 27% of patients on indapamide 2.5 mg and 5.0 mg, respectively. Other adverse reactions reported with antihypertensive/diuretics are intrahepatic cholestatic jaundice, sialadenitis, xanthopsia, photosensitivity, purpura, bullous eruptions, Stevens-Johnson syndrome, necrotizing angiitis, fever, respiratory distress (including pneumonitis), anaphylactic reactions, agranulocytosis, leukopenia, thrombocytopenia, aplastic anemia.

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References: 1. IMS National Prescription Audit (NPA), August 1991. Compared with year-to-date August 1991 percentage growth in new prescriptions among the 10 leading brands of diuretics. 2. Scott-Levin Physician Drug and Diagnosis Audit (PDDA). July 1990–June 1991.

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Assessment of Global and Regional Left Ventricular Performance at Rest and During Exercise After Thrombolytic Therapy for Acute Myocardial Infarction: Results of the Thrombolysis in Myocardial Infarction (TIMI) II Study

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Global and regional left ventricular performances were evaluated with equilibrium radionuclide angiocardiography in patients in the Thrombolysis in Myocardial Infarction (TIMI) II trial at the time of hospital discharge. Studies at rest were available in 1,162 (69%) of the invasive and 1,150 (69%) of the conservative strategy patients, and exercise studies in 1,133 (67%) of the invasive and 1,145 (69%) of the conservative patients. Repeat studies were performed at the time of 6-week follow-up. Global and regional ejection fraction at rest were both comparable in patients assigned to each of the treatment strategies. However, at the time of hospital discharge patients in the invasive strategy had normal exercise responses more frequently (29.7 vs 25.8% p = 0.01), greater peak exercise LV ejection fraction (54.8 ± 13.8% vs 53.1 ± 14.1%, p = 0.004), greater exercise — rest change in LV ejection fraction (3.7 ± 6.7% vs 2.7 ± 7.2%, p <0.001) and greater peak exercise infarct zone regional ejection fraction (53.2 ± 31.1% vs 50.3 ± 33.0%, p <0.001) than patients assigned to the conservative strategy. At 6-week follow-up these differences between treatment strategies were no longer evident. When data were restricted to those collected at comparable work loads, similar differences in hospital discharge exercise performance between invasive vs conservative strategy patients were observed. Thus, there is a small transient difference in exercise global and regional LV performance associated with an invasive as opposed to conservative strategy after thrombolytic therapy. These differences are noted at the time of hospital discharge but not at 6 weeks, and are unlikely to confer clinical benefit.

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Intravenously administered thrombolytic therapy currently is an established therapy for acute myocardial infarction. Such therapy has been associated with decreased mortality, presumably as a result of recanalization of the occluded infarct-related artery and reduction in infarct size.[1-9] The additional effects of mechanical revascularization, with either angioplasty or bypass surgery, on left ventricular (LV) function has been controversial.[10,11] Recently it has been suggested that discrepancies may exist between therapeutic effects on survival and LV performance.[12,13]

In the Thrombolysis in Myocardial Infarction (TIMI) II trial, patients presenting with ST-segment elevation recruited within 4 hours of the onset of chest pain were treated with intravenous recombinant tissue-type plasminogen activator (rt-PA), followed by intravenous heparin and aspirin and then randomly assigned to either an invasive or conservative treatment strategy.[10] The invasive strategy involved coronary arteriography within 18 to 48 hours of thrombolytic therapy, fol-

From the Maryland Medical Research Institute, Baltimore, Maryland. This study was supported by contracts from the National Heart, Lung, and Blood Institute, Bethesda, Maryland. Manuscript received April 25, 1991; revised manuscript received and accepted September 3, 1991.

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*Investigators and participating centers are listed in the Appendix.

lowed by percutaneous transluminal coronary angioplasty if anatomically suitable. In a substudy (TIMI IIA) previously reported, immediate angioplasty did not confer an advantage over either the delayed invasive or conservative strategies with respect to global or regional ventricular function.[11] In addition, TIMI II eligible patients were randomized to immediate intravenous β-blocker therapy or delayed therapy. Global and regional ejection fraction at rest or exercise at the time of hospital discharge and 6-week follow-up were comparable in the 2 groups.[14] The present report provides a detailed analysis of global and regional LV performance at rest and exercise, obtained by radionuclide ventriculography in the TIMI II patients.

METHODS

Patient population: A total of 3,339 patients were entered into the study: 1,681 were randomly assigned to the (delayed) invasive and 1,658 to the conservative strategies. Interpretable radionuclide exercise data were obtained at the time of hospital discharge in 1,133 (67%) of those assigned to the invasive strategy and 1,145 (69%) of those assigned to the conservative strategy. For the 6-week study, interpretable rest and exercise data were available in 1,089 (65%) invasive and 1,077 (65%) conservative strategy patients. The protocol hospital discharge study was obtained a mean of 9.3 days after randomization (range 2 to 38 days), whereas the follow-up "6-week" study was obtained 53.5 days after study entry (range 21 to 177).

Radionuclide ventriculography: Patients underwent equilibrium radionuclide ventriculographic study after modified in vivo red blood cell labeling according to standardized techniques.[15] To assure uniform methodology and quality, certification of all clinical sites was carried out before study inception. A detailed manual of operations outlined the method of data acquisition and transmittal to the core laboratory. Each clinical site submitted sample radionuclide studies to the core laboratory. Before clinical participation in the trial began, each site was certified by the core laboratory based on criteria for acceptable study quality. All radionuclide data were acquired in an electrocardiographic-synchronized frame mode in a 64 × 64 matrix. Data were acquired at 16 frames/RR interval. The unsmoothed studies were stored on magnetic tape or floppy disk and mailed to the radionuclide core laboratory at Yale University for further analysis. Studies analyzed in the core laboratory were identified only by code name and number. In the core laboratory studies were transcribed to a central computer for temporal and spatial filtering.

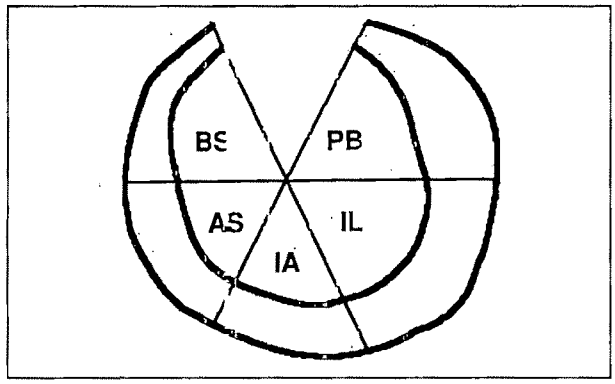


FIGURE 1. Diagramatic representation of orientation for regional left ventricular ejection fraction. Note the 60° pie involving the valve planes that are excluded from analysis. AS = apical septal; BS = basal septal; IA = inferoapical; IL = inferolateral; PB = posterolateral.

After ventriculograms were recorded in multiple views at rest, the patient was prepared for the exercise study. Exercise was performed using a bicycle ergometer in the supine position. Repeat baseline measurements at rest were obtained with the patient's feet attached to the pedals of the ergometer. For electrocardiographic monitoring during exercise, radiolucent electrodes were used for chest leads. The hospital discharge exercise test was limited to a maximal heart rate of 120 beats/min or a maximal work load of 67 W (400 kgf · m/min), and the development of angina or ST-segment depression, whichever came first. Global and regional ejection fraction was measured at each work load. The 6-week follow-up study was performed to symptom limitation.

Global LV ejection fraction was determined from the image recorded in the left anterior oblique position using previously validated and standardized programs.[16] The background-corrected volume curve was filtered to 4 Fourier harmonics. LV ejection fraction was determined from the fitted curve in the usual manner: end-diastolic counts minus end-systolic counts divided by end-diastolic counts.

The left anterior oblique LV end-diastolic region of interest was divided into 5 zones corresponding to the basal septal, apical septal, inferoapical, inferolateral and posterolateral regions. The area involving the valve planes was excluded (Figure 1). Regional ejection fraction was calculated from maximal and minimal counts in each region according to standard techniques.[15] For infarct zone regional ejection fraction, the electrocardiographic localization of infarction was related to the regions defined on the blood pool image, according to previously published techniques.[15] Inferior wall regional infarct zone ejection fraction was defined by averaging ejection fraction in the inferoapical and inferolateral zones. Anterior wall infarct regional ejection fraction was obtained from the average of data from the basal and apical septal zones. Lateral infarct regional ejection fraction was obtained from the posterolateral zone. The noninfarct zone regional ejection fraction was obtained by averaging regional ejection fraction from the remaining zones not involved in the infarct.

Protocol: The details of the TIMI II protocol have been described previously.[10] Briefly, the inclusion criteria were: age <76 years, chest discomfort suggestive of acute infarction lasting ≥30 minutes, ST-segment elevation >0.1 mV in 2 contiguous electrocardiographic leads, feasibility of instituting thrombolytic therapy within 4 hours of the onset of chest pain and patient consent. The rt-PA used (Activase®, Genentech) was produced by the suspension culture method. Total dose in the first 520 patients was 150 mg administered over 6

hours. Because of an unexpected high incidence of intracranial hemorrhage,[17] this dose was reduced to 100 mg in the remaining 2,819 patients.

Patients assigned to the invasive strategy were scheduled for coronary angiography, and angioplasty if suitable, within 18 to 48 hours after the initiation of rt-PA infusion. Angioplasty was performed as part of the same procedure unless the vessel was closed, the residual stenosis was not critical (<60%), the lesion had anatomically unsuitable features, or if abrupt closure of the involved vessel would cause catastrophic hemodynamic consequences. Bypass surgery was considered for patients with suitable indications. In patients assigned to the conservative strategy, cardiac catheterization and angioplasty were performed only if clinically evident ischemia occurred despite medical therapy during hospitalization, or if substantial ischemia was provoked during the predischarge exercise test. Coronary bypass surgery was performed in either group if there were appropriate clinical or protocol indications and coronary anatomy was unsuitable for angioplasty.

The β-blocker randomization involved immediate versus delayed β-blocker therapy.[10,14] In those assigned to immediate intravenous β-blocker therapy, 15 mg of metoprolol was given in three 5 mg intravenous injections at 2-minute intervals, followed by oral metoprolol (50 mg twice a day on the first day and 100 mg twice a day thereafter), if tolerated. Those assigned to deferred β-blocker therapy began therapy with 50 mg of oral metoprolol twice a day on day 6 and 100 mg twice a day thereafter. Thus most of the patients were receiving oral β-blocker therapy at the time of initial and follow-up radionuclide evaluation. Patients already receiving a β-blocker, verapamil or diltiazem at the time of entry and those with relative contraindications to the use of β blockers were excluded from this portion of the trial.[14]

Statistical analysis: The p values for comparison of percentages were calculated using standard z tests.[18] To adjust for multiple comparisons, p values between 0.01 and 0.001 for 2-sided tests have been specified as providing some evidence of differences and p values <0.001 as providing strong evidence of differences. Distributions of categorical variables are compared with standard chi-square tests for homogeneity of proportions.[18]

To account for all patients entered into the study, patients who died before performance of exercise radionuclide ventriculography are regarded as having the worst possible outcome, and patients alive at the time of exercise radionuclide ventriculography who could have been performed but were not able to complete interpretable studies are regarded as unlikely to have had the best possible outcome. The analyses most resistant to biases associated with missing radionuclide ventriculography measurements are the comparison of the proportions of patients with the best treatment outcome (increase in ejection fraction with exercise ≥5%) and the comparison of the entire distribution of treatment outcome categories.

Continuous variables are compared with standard paired and unpaired *t* tests.[19] To summarize the effects of treatment on regional ejection fraction for the ventricular segments associated with infarct locations or remote from infarct locations, a regression analysis was performed with the following model: regional ejection fraction = a constant intercept plus treatment effect plus infarct-related artery effect plus random error.[15,20] Treatment effects analyzed in this model compared invasive and conservative strategies. When comparing the invasive and conservative strategies, this adjusted regional ejection fraction reflects the infarct regional ejection fraction with allowance made for specific infarct location.

All analyses were performed using the Statistical Analysis Systems (SAS) computer programs,[21] with an analysis file created in September 1990.

RESULTS

Study population: Baseline and peak exercise LV function data at hospital discharge were available in 2,278 patients, whereas 6-week follow-up data were available in 2,166. Exercise studies were not performed at the time of hospital discharge in 372 patients and at 6-week follow-up in 417 patients assigned to the invasive strategy. In patients assigned to the conservative strategy, exercise studies were not done in 315 at the time of hospital discharge and 407 at 6 weeks. A comparison of the patients with LV function data analyzed for both hospital discharge and follow-up radionuclide studies with those not included in both analyses indicated that patients not undergoing radionuclide evaluations expectedly formed a higher risk group. Patients not included in both analyses were older (58.2 vs 55.3 years, p <0.001) and more frequently had: prior infarction (16.6 vs 11.4%, p <0.001), rales >⅓ lung field (5.5 vs 2.6%, p <0.001), pulmonary edema 1.6 vs 0.5%, p = 0.001), cardiogenic shock 2.1 vs 0.9%, p = 0.003), history of congestive heart failure (4.1 vs 1.5%, p <0.001) and history of diabetes mellitus (16.0 vs 10.5%, p <0.001).

Death was the reason for studies not being performed in 148 patients at hospital discharge and 175 at 6 weeks. Among surviving patients, most frequent causes for nonperformance of studies at the time of hospital discharge were cardiac and noncardiac medical conditions, logistic difficulties (e.g., laboratory unavailability) and cardiac surgery; however, at the time of 6-week follow-up, logistic difficulties (including lack of patient transportation) accounted for a large proportion of nonperformance. Cardiac causes and cardiac surgery were much less common as reasons for nonperformance at 6-week follow-up then at hospital discharge. The distribution of reasons for nonperformance of studies was different at hospital discharge versus 6 weeks (p <0.001). However, reasons for study nonperformance were similar for invasive and conservative strategies at either time.

Of those conservative strategy patients with available LV function data, 9.9% underwent revascularization with either angioplasty or bypass surgery before hospital discharge and 14.1% underwent revascularization between hospital discharge and 6-week follow-up.

Resting left ventricular function (Table I): At rest, global ejection fraction was similar in patients random-

ized to the invasive and conservative strategies. There were no significant differences in the hospital discharge (50.8 ± 12.7 vs 50.2 ± 12.7) and 6-week (50.5 ± 13.2 vs 50.4 ± 12.8) data, respectively. Individual regional ejection fractions were similar in both strategies at hospital discharge and at 6 weeks. When infarct zone regional ejection fraction was adjusted to account for the difference in distribution of locations of infarction in each group, the treatment difference was small at hospital discharge (49.6 ± 28.6 vs 48.0 ± 29.9, p = 0.01) and not significant at 6 weeks.

Exercise function (Tables II and III): At hospital discharge, there was a significant difference in the distribution of exercise responses between patients assigned to invasive and conservative strategies (Table II). When all patients were accounted for, including those in whom studies were not obtained, those who were deceased and those whose studies were not interpretable, 29.7% of patients in the invasive strategy had a normal global ejection fraction response (an increase in global ejection fraction of ≥5%) compared with 25.8% of patients in the conservative strategy (p = 0.01). A smaller percent-

TABLE I Resting Global and Regional Left Ventricular Ejection Fraction at Hospital Discharge and Six-Week Follow-Up of Invasive and Conservative Strategies

	Hospital Discharge			Six Weeks		
	Invasive (n = 1,681)	Conservative (n = 1,658)	p Value	Invasive (n = 1,681)	Conservative (n = 1,658)	p Value
Global LVEF	50.8 ± 12.7 (1,177)	50.2 ± 12.7 (1,156)	0.28	50.5 ± 13.2 (1,188)	50.4 ± 12.8 (1,157)	0.78
Regional LVEF						
Basal septal	38.5 ± 16.3 (1,162)	38.0 ± 16.4 (1,150)	0.43	38.6 ± 16.1 (1,180)	38.7 ± 15.8 (1,146)	0.94
Apical septal	40.9 ± 17.6 (1,162)	39.6 ± 17.9 (1,150)	0.07	39.7 ± 17.7 (1,180)	39.2 ± 17.7 (1,146)	0.55
Inferoapical	49.4 ± 19.1 (1,162)	47.5 ± 19.2 (1,150)	0.02	48.6 ± 19.5 (1,180)	48.0 ± 19.5 (1,146)	0.42
Inferolateral	60.0 ± 17.7 (1,162)	59.1 ± 17.5 (1,150)	0.25	59.7 ± 18.1 (1,180)	59.5 ± 17.8 (1,146)	0.81
Posterolateral	66.3 ± 16.4 (1,162)	67.1 ± 16.0 (1,150)	0.61	68.0 ± 16.4 (1,180)	67.8 ± 16.1 (1,146)	0.74
Adjusted infarct zone						
Regional LVEF*	49.6 ± 28.6 (1,162)	48.0 ± 29.9 (1,150)	0.01	51.2 ± 29.7 (1,180)	50.4 ± 30.5 (1,146)	0.22

*Value adjusted for distribution of infarct artery in each treatment group ( ) = number of patients with studies obtained at hospital discharge and at 6 weeks; differences in denominators are due to differing numbers of interpretable studies (technical factors).
LVEF = left ventricular ejection fraction (mean ± standard deviation).

TABLE II Distribution of Peak Global Ejection Fraction Responses in All TIMI II Patients

	Hospital Discharge				Six Weeks			
	Invasive (n = 1,681)		Conservative (n = 1,658)		Invasive (n = 1,681)		Conservative (n = 1,658)	
	No.	%	No.	%	No.	%	No.	%
LVEF change								
Increase ≥ 5%	500	29.7	427	25.8	452	26.9	409	24.7
No change	537	32.0	561	33.8	469	27.9	480	29.0
Decrease ≥ 5%	96	5.7	157	9.5	168	10.0	188	11.3
Status of other patients								
Exercise test but no exercise LVEF	176	10.5	198	11.9	175	10.4	174	10.5
Resting test but no exercise LVEF	177	10.5	137	8.3	54	3.2	60	3.6
No resting test	113	6.7	112	6.8	272	16.2	263	15.9
Dead (≤ 21 days for hospital discharge) (≤ 70 days for follow-up)	82	4.9	66	4.0	91	5.4	84	5.1
Total	1,681	100.0	1,658	100.0	1,681	100.0	1,653	100.0

When the proportion of patients with a left ventricular ejection fraction increase ≥ 5% were compared, p = 0.01 at hospital discharge and p = 0.14 at 6 weeks.
LVEF = left ventricular ejection fraction; TIMI = Thrombolysis in Myocardial Infarction trial.

TABLE III Regional and Global Left Ventricular Ejection Fraction Exercise Data at Hospital Discharge and Six-Week Follow-Up

	Hospital Discharge			Six Weeks		
	Invasive (n = 1,133)	Conservative (n = 1,145)	p Value	Invasive (n = 1,089)	Conservative (n = 1,077)	p Value
Baseline LVEF	51.0 ± 12.2	50.4 ± 12.5	NS	50.9 ± 12.5	50.4 ± 12.2	NS
Peak exercise LVEF	54.8 ± 13.8	53.1 ± 14.1	0.004	53.8 ± 14.9	52.6 ± 14.2	0.06
Δ LVEF (peak-baseline)	3.7 ± 6.7	2.7 ± 7.2	<0.001	2.9 ± 8.0	2.2 ± 7.9	0.03
(Adjusted)* peak ex. infarct zone regional LVEF	53.2 ± 31.1	50.3 ± 33.0	<0.001	51.1 ± 32.2	49.5 ± 33.4	0.04

*Adjusted for distribution of infarct artery in each treatment group.
Values are expressed as mean ± standard deviation.
ex. = exercise; LVEF = left ventricular ejection fraction; NS = not significant; Δ = mean change.

TABLE IV Regional and Global Left Ventricular Ejection Fraction Exercise Data at Hospital Discharge and Six-Week Follow-Up Obtained at Comparable Work Loads

	Hospital Discharge			Six Weeks		
	Invasive (n = 796)	Conservative (n = 778)	p Value	Invasive (n = 796)	Conservative (n = 778)	p Value
Baseline LVEF	51.3 ± 12.0	50.5 ± 12.1	NS	51.4 ± 12.2	50.4 ± 12.0	NS
Peak exercise	55.2 ± 13.4	53.4 ± 13.7	0.01	54.3 ± 13.9	52.6 ± 13.5	0.02
Δ LVEF (peak ex.)	4.0 ± 6.6	2.9 ± 7.1	0.002	2.9 ± 7.1	2.2 ± 6.6	0.04
Peak exercise infarct zone regional LVEF*	53.2 ± 30.4	50.2 ± 31.5	0.001	51.6 ± 30.5	50.2 ± 31.5	NS

*Adjusted for distribution of infarct artery in each treatment group.
Abbreviations as in Table III.

age of patients in the invasive strategy (5.7%) than in the conservative strategy (9.5%) demonstrated a significant decrease in LV ejection fraction of ≥5%. In contrast, at 6 weeks these differences were no longer noted (26.9 vs 24.7% for an increase in ejection fraction and 10.0 vs 11.3% for a decrease in ejection fraction between invasive and conservative groups, respectively). When these distributions were evaluated in only those in whom exercise data were available at hospital discharge or at 6 weeks, the same observation was evident at hospital discharge (i.e., more patients in the invasive group had a normal exercise LV functional response), but was still absent at 6 weeks. For patients assigned to either strategy, the predominant response to exercise was no major change (increase or decrease) in ejection fraction on hospital discharge and 6-week studies.

At the time of hospital discharge there was a small but significant increase in global ejection fraction with exercise in patients assigned to the invasive compared to the conservative strategy, whereas there was no difference in ejection fraction at rest (Table III). Similar differences were noted for the change in ejection fraction from rest to exercise, and infarct zone regional ejection fraction during exercise. At 6-weeks, these differences had largely disappeared.

Clinical exercise results: Of the 2,652 patients who performed hospital discharge exercise studies (2,502 within 14 days of study entry), 2,140 (2,026 within 14 days of study entry) had both nuclear and electrocardiographic data interpreted centrally, whereas 138 (125 within 14 days) had central interpretations of LV function but not the electrocardiogram, 351 (329 within 14 days) had interpretation of the electrocardiogram but not the radionuclide angiocardiogram and 23 (22 within 14 days) had neither. Of the 1,063 invasive strategy patients with both sets of data interpreted centrally, 112 (10.5%) had ischemic ST-segment responses compared with 162 (15.0%) of the 1,077 conservative strategy patients (p = 0.002). Among the 1,309 invasive strategy patients with exercise studies, 57 (4.4%) had ischemic pain, and 76 (5.7%) of the 1,343 conservative strategy patients had ischemic pain on exercise (p = 0.12). Analyses of the hospital discharge data were similar whether restricted to patients who exercised within 14 days of study entry or inclusive of later studies. Of the 995 invasive strategy patients with both 6-week radionuclide angiocardiograms and electrocardiograms centrally interpreted, 141 (14.2%) had ischemic ST-segment responses; 164 (16.8%) of the 977 conservative strategy (p = 0.11) had such ST-segment responses. Among the 1,263 invasive strategy patients with 6-week exercise studies, 75 (5.9%) had ischemic pain, and 95 (7.6%) of the 1,251 conservative strategy patients had pain (p = 0.10).

Exercise at comparable work loads: One possible explanation for different results at hospital discharge and at 6 weeks is the different work loads in the 2 studies. Because data were obtained at each work load of the graded supine exercise study, it was possible to evaluate a subgroup of patients in whom both exercise studies were performed and in whom LV performance could be compared at similar work loads. This was done in a subgroup of 796 patients in the invasive and 778 patients in the conservative strategies (Table IV). At hospital discharge, there was no difference in baseline ejection fraction between the 2 groups. However, there were small but significant differences in the absolute exercise ejection fraction, increase in global ejection fraction and exercise regional infarct zone ejection fraction between patients assigned to the invasive versus the conservative strategies. When the same patients were evaluated at 6 weeks at the same work load, these differences were diminished and no longer significant.

Absolute changes between hospital discharge and six-week studies: The differences between the 2 strategies noted over the time interval between hospital dis-

TABLE V Absolute Changes in Global and Regional Exercise Left Ventricular Ejection Fraction from Hospital Discharge to Six-Week Follow-Up in Patients with Both Studies at Comparable Work Loads

Comparable Exercise Work Loads at Discharge and Six Weeks	Invasive (n = 1,681)			Conservative (n = 1,658)		
	No.	Mean Change*	p Value	No.	Mean Change*	p Value
Global LVEF	796	−0.94	0.002	779	−0.71	0.02
Adj. regional infarct zone LVEF	779	−1.07	0.02	768	0.80	0.08
Adj. regional non-infarct zone LVEF	779	−0.99	0.01	766	−0.70	0.09

*Mean of (6-week-hospital discharge) data.
Adj. = adjusted for distribution of infarct artery in each treatment group. LVEF = left ventricular ejection fraction.

charge and 6 weeks could be due to improvement in patients assigned to the conservative strategy or worsening in patients assigned to the invasive strategy, or both, or comparable directional changes of different magnitude. To evaluate these possibilities, invasive and conservative strategy patients' absolute values of global, regional infarct zone and regional noninfarct zone ejection fractions were compared at hospital discharge and at 6 weeks. This was done for all patients with both studies as well as those with data available at comparable work loads in the 2 studies (Table V). In patients assigned to the invasive strategy, at comparable work loads, there was a significant decrement in global ejection fraction as well as a lesser decrement in regional infarct and noninfarct zone ejection fractions between hospital discharge and 6 weeks. This pattern was much less distinct in patients assigned to the conservative strategy.

Interval events: The occurrence and potential impact on exercise LV function of interval events between studies (such as myocardial infarction, angioplasty or bypass surgery) in patients in both invasive and conservative strategies also were examined. In the interval between the hospital discharge and 6-week studies, 94 patients assigned to the conservative and 20 assigned to the invasive strategy underwent angioplasty, 48 conservative and 27 invasive strategy patients underwent bypass surgery, and 18 conservative and 10 invasive strategy patients had myocardial infarction. None of the interval events occurred with sufficient frequency to be important in the analysis.

Subgroup analyses: Although all major analyses were based on treatment strategy randomization, several post hoc subgroup analyses were undertaken. With respect to a history of prior myocardial infarction, those patients with prior infarction were associated with a lower global and regional infarct zone ejection fraction at hospital discharge and a low regional infarct zone ejection fraction at peak exercise at 6 weeks. However, conclusions regarding therapeutic strategy effects were the same whether or not prior infarction had occurred. Likewise, with respect to site of infarction, patients with anterior wall infarcts not surprisingly demonstrated significantly lower global and infarct zone regional ejection fraction at rest and peak exercise at both hospital discharge and at 6 weeks. Once again, conclusions concerning therapeutic strategy effects were the same in patients with and without anterior wall infarction.

In patients in the invasive strategy undergoing protocol catheterization, LV function was related to TIMI perfusion grade immediately after protocol angioplasty (n = 1,184 patients). At hospital discharge those with TIMI grade 3 perfusion had higher resting global LV ejection fraction (52.2 ± 12.4 vs 46.4 ± 13.2, p <0.001) and infarct zone regional ejection fraction (50.7 ± 28.6 vs 43.9 ± 20.6, p <0.001) than patients with perfusion grades <3. Comparable data were noted at 6 weeks (52.2 ± 12.6 vs 45.9 ± 14.2, p <0.001; 52.4 ± 30.0 vs 44.9 ± 21.6, p <0.001, respectively). With peak exercise at hospital discharge, those with TIMI grade 3 perfusion also had a higher peak global ejection fraction (56.8 ± 13.0 vs 49.0 ± 14.6, p <0.001) and regional infarct zone ejection fraction (55.1 ± 29.8 vs 46.2 ± 21.7, p <0.001) than those with TIMI perfusion grade <3. Comparable results again were noted at 6 weeks.

DISCUSSION

The present study demonstrates that there are no differences in global and regional LV function at rest between patients receiving thrombolysis assigned to conservative or invasive strategies, either at the time of hospital discharge or at 6-week follow-up. Hospital discharge evaluation during exercise revealed small but statistically significant differences in both regional and global LV ejection fraction in patients assigned to the invasive strategy compared with those assigned to the conservative strategy. Although these changes are statistically significant, they are modest in magnitude and would be expected to have relatively limited clinical or pathophysiologic impact. Furthermore, differences observed at the time of hospital discharge between patients in the 2 treatment strategies were no longer apparent at the time of follow-up evaluation at 6 weeks.

Why the small advantage in exercise response associated with the invasive strategy was transient bears further consideration. The reduction in differences does not appear attributable to the greater work load, and hence increased physical stress on the maximal symptom-limited exercise study at 6-week follow-up (Table IV). The occurrence of myocardial infarction or revascularization between hospital discharge and 6-week studies were too infrequent to be important factors. Between hospital discharge and 6 weeks, there was a significant decrease in global ejection fraction and noninfarct zone regional exercise ejection fraction in patients assigned to the invasive strategy (Table V). In patients in the conservative strategy there was a trend in a similar direction, but of lesser magnitude. This suggests that the difference noted over time between the 2 strategies results at least in part from a greater decrement in regional and global function in patients in the invasive strategy. Observations at hospital discharge may be the result of nonspecific factors such as enhanced catecholamine effects, which may be transiently more marked in those assigned to the invasive strategy. Alternatively, mechanical revascularization may result in an augmentation of blood flow that may transiently benefit regional and global LV function. These effects may have a lesser impact over time when there has been further healing or ventricular remodeling.[22]

The predominant exercise response in TIMI II was one of no change in either global or regional LV ejection fraction at both hospital discharge and 6-week follow-up. This is in contrast to observations on exercise LV function obtained in the prethrombolytic era, when a decrease in exercise ejection fraction was a much more common phenomenon.[23-30] Guerci et al[31] also studied patients treated with rt-PA in a placebo-controlled trial. They noted significantly higher ejection fraction at rest in patients randomized to thrombolytic therapy as opposed to placebo. A second randomization involved angioplasty on the third hospital day. Angioplasty improved exercise LV ejection fraction response

and also reduced the incidence of clinical ischemia, but had no effect on LV ejection fraction at rest. The protocol design in Guerci's study is different from TIMI II in that it was placebo-controlled. Although the increase in ejection fraction from rest to exercise in the angioplasty group appears larger than noted in TIMI II, the level of statistical significance is comparable. In addition, Guerci et al evaluated relatively small numbers of patients (34 and 35 patients in the angioplasty and conservative groups, respectively). Their observations also were made at hospital discharge and no statements can be made concerning the persistence of the differences observed.

Most of the TIMI II patients were receiving oral β blockers at the time of exercise testing. This may have blunted ventricular responses to exercise. It is also possible that other measures, such as ventricular volumes or ventricular shape analysis, might have demonstrated intergroup differences relating to architectural remodeling. However, such more complex and sophisticated analyses were beyond the scope of this large multicenter trial.

Subgroup analyses provided expected results with respect to history of prior infarction and infarct site. The influence of TIMI grade 3 perfusion was associated with substantial sustained improvement in global and regional LV function at rest and during exercise. This is similar to previous investigations.[32]

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Influence of Collateral Filling of the Occluded Infarct-Related Coronary Artery on Prognosis After Acute Myocardial Infarction

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Previous studies showed that long-term morbidity and mortality after acute myocardial infarction (AMI) are influenced by the presence or absence of anterograde flow in the infarct artery. In comparison with patients with anterograde flow, those whose infarct artery remains occluded are more likely to have unstable angina, recurrent AMI, congestive heart failure and sudden death. This study was performed to assess the influence of collateral filling of the infarct artery on long-term morbidity and mortality in surviving patients of initial AMI in whom the infarct artery was occluded. Over a 12.5-year period, 146 subjects (108 men and 38 women, aged 25 to 76 years) with AMI, no anterograde flow in the infarct artery, and no disease of other coronary arteries were medically treated and followed for 42 ± 28 (mean ± standard deviation) months. Of these subjects, 120 had angiographic evidence of collateral filling of the infarct artery (group I), whereas the remaining 26 did not (group II). The groups were similar in age, sex, cardioactive medications, left ventricular performance and infarct artery. They were also similar in incidence of unstable angina (19% of group I, 31% of group II; p = not significant [NS]), recurrent AMI (12% of group I, 8% of group II; p = NS), congestive heart failure (16% of group I, 12% of group II; p = NS) and cardiac death (16% of group I, 19% of group II; p = NS). Thus, angiographic evidence of collateral filling of the infarct artery in surviving patients of AMI exerts no demonstrable influence (beneficial or detrimental) on long-term morbidity or mortality.

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The influence of coronary collateral circulation on morbidity and mortality in patients with atherosclerotic coronary artery disease has been a subject of controversy for >5 decades. Based on pathologic studies performed long before coronary arteriography was available, Blumgart et al[1] suggested that coronary collateral vessels exerted a beneficial influence on subjects with angina pectoris and acute myocardial infarction (AMI). In contrast, Wiggers[2] argued that collateral vessels exerted little effect on morbidity or mortality in these patients. Subsequent studies provided conflicting data on the benefit of coronary collateral vessels to patients with various manifestations of coronary artery disease. In subjects after AMI, some reports suggested that collateral filling of the infarct artery improved survival,[3,4] whereas others[5,6] did not.

In previous studies, we showed that the presence or absence of anterograde flow in the infarct artery of survivors of AMI strikingly influenced morbidity and mortality during long-term follow-up.[7,8] Patients with disease of only the infarct artery and with residual anterograde perfusion of it had little morbidity and no mortality during an average follow-up of almost 4 years, whereas those without residual anterograde perfusion frequently had unstable angina, recurrent AMI, congestive heart failure and sudden death.[7] The present study was performed to assess the effect, if any, of collateral filling of the infarct artery on morbidity and mortality in surviving patients of initial AMI with only an occluded infarct artery who were managed medically.

METHODS

Patient population: We reviewed the results of all cardiac catheterizations at Parkland Memorial Hospital, Dallas, Texas, from July 1978 to December 1990. Of 4,451 patients, 189 were studied 1 to 150 days after their first AMI and were found to have no anterograde flow in the infarct artery and no disease of the other arteries. Thirteen underwent coronary angioplasty, and 24 had coronary artery bypass surgery for medically refractory angina; these subjects were excluded from further analysis. Long-term follow-up information was not available in 6 of the 152 patients treated medically (4 with and 2 without collateral filling of the infarct artery). The remaining 146 subjects (108 men, 38 women, aged 25 to 76 years) form the basis of this report.

At coronary arteriography, 120 subjects (group I) had collateral filling of the infarct artery, whereas the remaining 26 (group II) did not. Of the 120 subjects in group I, 25 (21%) underwent catheterization because they were ≤40 years old, 8 (7%) as a routine after in-

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travenous thrombolytic therapy, 65 (54%) because of postinfarction angina, 16 (13%) because of a positive submaximal exercise test result, and 6 (5%) for other reasons. Of the 26 subjects in group II, 4 (15%) underwent catheterization because they were ≤40 years old, 5 (19%) as a standard procedure after intravenous thrombolytic therapy, 12 (46%) because of postinfarction angina, 3 (12%) because of a positive submaximal exercise test result, and 2 (8%) for other reasons. The records of each patient were reviewed, and each surviving subject was interviewed. For patients who died, the immediate next of kin was interviewed.

Variables assessed: At the time of catheterization, left ventricular volumes and ejection fraction were quantitated according to standard techniques.[9,10] Selective coronary arteriography was performed, and presence or absence of collateral filling of the infarct artery was noted. As previously defined,[11,12] coronary collaterals were said to be present if the portion of artery distal to the site of occlusion was filled by accessory blood vessels or during contrast injection of a contralateral artery, or both. During subsequent follow-up, presence of several risk factors for atherosclerotic cardiovascular disease (hypertension, cigarette smoking, diabetes mellitus and serum cholesterol >270 mg/dl) was noted, and records were kept of each patient's cardioactive medications. The occurrence of morbid events, including hospitalization for unstable angina, recurrent AMI or congestive heart failure, and of death was noted. The specific criteria for these diagnoses were described previously.[7,13,14]

Statistical methodology: All data are reported as mean ± 1 standard deviation. The characteristics of the 2 groups were compared using the chi-square test for categorical variables, and Student's *t* test for continuous variables. For all analyses, a p value <0.05 was considered significant.

TABLE I Comparison of the Two Patient Groups

	Group I (n = 120) Collaterals	Group II (n = 26) No Collaterals	p Value
Age (yrs)	48 ± 11	51 ± 11	NS
Number of men (%)	89 (74)	19 (73)	NS
Number of days from AMI to catheterization	29 ± 29	19 ± 15	NS
Risk factors for atherosclerotic cardiovascular disease (%)			
Systemic hypertension	57 (48)	10 (38)	NS
Cigarette smoking	80 (67)	19 (73)	NS
Diabetes mellitus	20 (17)	7 (27)	NS
Serum total cholesterol >270 mg/dl	29 (24)	4 (15)	NS
Duration of follow-up (mos)	42 ± 28	42 ± 28	NS
Medications after AMI (%)			
Calcium antagonists	50 (42)	10 (38)	NS
β blockers	56 (47)	7 (27)	NS
Long-acting nitrates	69 (58)	14 (54)	NS
Aspirin	50 (42)	12 (46)	NS
Left ventricular volumes			
End-diastolic volume (ml/m^2)	73 ± 19	70 ± 28	NS
End-systolic volume (ml/m^2)	36 ± 15	37 ± 28	NS
Ejection fraction	0.53 ± 0.11	0.51 ± 0.15	NS
Infarct artery (%)			
Left anterior descending	39 (33)	13 (50)	NS
Left circumflex	20 (17)	5 (19)	NS
Right	61 (50)	8 (31)	NS
Morbid events (%)			
Unstable angina	23 (19)	8 (31)	NS
Recurrent AMI	14 (12)	2 (8)	NS
Congestive heart failure	19 (16)	3 (12)	NS
Mortality (%)			
Cardiac	19 (16)	5 (19)	NS
Total	23 (19)	5 (19)	NS

AMI = acute myocardial infarction; NS = not significant.

RESULTS

Patients with angiographic evidence of collateral filling of the infarct artery (group I, n = 120) were similar to those without collateral filling (group II, n = 26) in age, sex, risk factors for atherosclerotic cardiovascular disease, cardicactive medications, infarct artery, left ventricular volumes and ejection fraction, time interval from infarction to catheterization, and duration of follow-up (Table I). The incidence of cardiac morbidity (unstable angina, recurrent AMI and congestive heart failure) and mortality was similar for groups I and II (Table I).

DISCUSSION

Previous studies provided conflicting data on the influence of coronary collateral vessels on morbidity and mortality in patients with coronary artery disease. In surviving patients of AMI, some reports suggested that collateral vessels were beneficial, whereas others showed that collateral filling of the infarct artery did not influence the postinfarction course or, in some cases, was deleterious. Webster et al[3] and Hansen[4] showed that survival was substantially improved in those with collateralization of occluded or narrowed coronary arteries. However, Habib et al[5] showed that collateral filling of the infarct artery improved left ventricular performance but exerted no effect on survival 6 weeks or 6 months after AMI. Furthermore, Gohlke et al[6] suggested that collateral filling of the distal left anterior descending coronary artery after AMI exerted a detrimental influence on survival. In light of this controversy, we sought to assess the influence (beneficial or detrimental) of collateral filling of the infarct artery on morbidity and mortality in patients after AMI who had only an occluded infarct artery.

Our data, obtained from 146 patients with AMI and only an occluded infarct-related coronary artery, show that long-term morbidity and mortality were not influenced by angiographically visible collateral filling of the infarct artery. During long-term follow-up with medical therapy, unstable angina, recurrent AMI and congestive heart failure occurred with similar frequency in patients with and without collateral filling of the infarct artery (Table I). Death from all causes occurred in 19% of patients with and in 19% of those without collateral filling of the infarct artery (p = not significant), and cardiac death occurred in 16% of those with and in 19% of those without angiographically visible collateral filling

of the infarct artery (p = not significant) (Table I). Thus, angiographic evidence of collateral filling of the infarct artery after AMI exerts no demonstrable influence (beneficial or detrimental) on subsequent morbidity or mortality.

Our study has certain limitations. First and most importantly, it is a retrospective assessment of patients with AMI and angiographic evidence of only an occluded infarct-related artery. Our results need to be confirmed by a properly performed prospective evaluation. Second, although we included all subjects who had an AMI and only an occluded infarct-related artery over a 12.5-year period, not all patients with AMI at our hospital during that time had catheterization. Although unlikely, we cannot exclude the possibility that our results may have been different if all patients had undergone catheterization after AMI. However, our study has certain strengths. It provides follow-up data over an extended period of time (42 ± 28 months) on a large cohort of patients, with 39 followed for >5 years.

In conclusion, whereas anterograde perfusion of the infarct artery after AMI dramatically diminishes the occurrence of unstable angina, recurrent AMI, congestive heart failure and sudden death,[7,8] collateral filling of the infarct artery does not reduce the incidence of long-term morbidity or mortality. The restoration of anterograde flow (pharmacologically or mechanically) may be beneficial even if it is accomplished hours to days after the acute event even in patients with collateral filling of the infarct artery. This possibility needs confirmation in a properly designed prospective clinical trial.

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Predicting Arrhythmic Events After Acute Myocardial Infarction Using the Signal-Averaged Electrocardiogram

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To determine if the signal-averaged (SA) electrocardiogram (ECG) predicts the occurrence of sustained ventricular arrhythmia and sudden death after acute myocardial infarction, 182 consecutive patients underwent systematic noninvasive testing, including the SAECG. Seventy-one patients (39%) had an abnormal SAECG. The presence of an abnormal SAECG was not related to underlying left ventricular dysfunction or any other clinical or measured variable. There were 16 end points (sustained ventricular arrhythmia or sudden cardiac death) during 14-month follow-up. The SAECG was a significant predictor of these events ($p < 0.02$), and an abnormal SAECG conferred a 2.7-fold increase in risk. The risk associated with an abnormal SAECG was independent of both left ventricular function and ventricular arrhythmia on Holter ECG. The SAECG had excellent negative predictive accuracy (95%), but the positive predictive accuracy was low (15%). When the results of the SAECG were combined with the results of the Holter ECG, a group of very high-risk patients was identified; at 18 months, the presence of abnormal SAECG and Holter ECG was associated with a risk of 26% compared with only 4% if both tests were normal. Furthermore, all published studies with a similar design were pooled for meta-analysis. The meta-analysis revealed a sixfold increase in risk, independent of left ventricular function, and an eightfold increase in risk, independent of Holter results when the SAECG was abnormal. The SAECG is a noninvasive test that can rapidly and easily provide potent prognostic information regarding the risk of sustained ventricular arrhythmias for patients after myocardial infarction.

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Sustained ventricular tachyarrhythmias are responsible for up to 50% of the mortality after myocardial infarction.[1] Thus, a great deal of effort has been made to identify high-risk groups in whom further investigation or intervention is needed. It is well established that a low left ventricular ejection fraction and frequent or repetitive ventricular arrhythmia on a 24-hour electrocardiogram (ECG) are potent predictors of sudden and nonsudden cardiac mortality after myocardial infarction.[2-4] Patients with coronary heart disease and sustained ventricular tachyarrhythmias have a high prevalence of abnormal signal-averaged ECGs (SAECGs).[5-7] Recent studies after myocardial infarction suggested that the SAECG can be used to predict which patients are at high risk for sustained ventricular arrhythmias or sudden death.[8-12]

Because the SAECG appears to provide unique information regarding the electrical substrate necessary for ventricular tachyarrhythmias, we prospectively studied a consecutively enrolled sample of patients after myocardial infarction with the following primary hypothesis: the SAECG predicts the occurrence of sustained ventricular arrhythmia and sudden cardiac death after myocardial infarction, and predicts risk, independent of left ventricular dysfunction or spontaneous ventricular arrhythmia on the Holter ECG. In addition, we had the following secondary objectives: (1) to determine whether the prevalence of abnormal SAECGs is related to the site of myocardial infarction, the degree of left ventricular dysfunction, or the amount of ventricular arrhythmia detected by Holter ECG; (2) to examine whether the total filtered QRS duration on the SAECG, or the measurement of late potential duration and voltage is superior for predicting sustained ventricular arrhythmia; (3) to evaluate the combined use of the SAECG, the left ventricular ejection fraction and ventricular arrhythmias on Holter ECG for predicting arrhythmic risk; and (4) to perform a meta-analysis of all published prospective studies to determine the current state of knowledge concerning the independent prognostic value of the SAECG after myocardial infarction.

METHODS

Patients: All patients with an acute myocardial infarction presenting to Columbia-Presbyterian Medical Center were eligible for enrollment. The study was approved by the institutional review board of Columbia-Presbyterian Medical Center. Cardiac Arrhythmia

Suppression Trial criteria[13] were used to define myocardial infarction. The major diagnostic criteria included any 2 of the following: symptoms typical of an acute myocardial infarction (>30 minutes of chest discomfort, and so forth); enzymatic criteria (i.e., total creatine phosphokinase ≥1.5 times the upper limit of normal, and creatine kinase-MB >5% of total creatine phosphokinase); and ECG criteria (new abnormal Q-wave, ST segment or T-wave changes). Patients were excluded from the study if they would not be available for follow-up in this country or if their ECG had bundle branch block (see later). Patients enrolled in this study were not participating in the Cardiac Arrhythmia Suppression Trial.

Study procedures: On enrollment, the patients' demographics, medical history and 12-lead ECG data were recorded. Patients underwent additional evaluation with 24-hour Holter recording, determination of left ventricular (LV) ejection fraction, and a SAECG. All noninvasive tests were performed before hospital discharge a mean of 9.5 ± 5 days after myocardial infarction.

Two-channel (modified V_2 and V_5) 24-hour Holter recordings were obtained. All tapes were analyzed by computer (Marquette 8000) and manually overread by physicians. The following ventricular arrhythmia data were carefully quantified for each tape: number of ventricular premature complexes (VPCs) per hour; number of paired VPCs per 24 hours; and number of runs of unsustained ventricular tachycardia (≥3 beats at a rate of >100 beats/min) per 24 hours. Our a priori definition of an abnormal Holter recording was ≥10 VPCs/hour, ≥1 paired VPC/24 hours, or ≥1 run of unsustained ventricular tachycardia/24 hours.

LV ejection fraction was determined by radionuclide methods when possible. The a priori definition of LV dysfunction was ejection fraction <0.40. This value was used in other large postmyocardial infarction studies.[2,4]

An SAECG was recorded in the patients. The methods for obtaining the SAECG and time-domain analysis were previously published.[14] Briefly, the SAECG was recorded from 3 orthogonal leads to a preprocessing noise value in the TP segment of ≤0.3 μV using a Corazonix Predictor (Oklahoma City, Oklahoma). The 3 leads were combined into a vector sum that was then processed with a bidirectional Butterworth filter at a bandpass setting of 40 to 250 Hz. The QRS onset and offset were set by computer algorithm and manually overread by an observer unaware of the patient's endpoint status. Three measurements were obtained from the amplified and filtered vector composite from the 3 orthogonal leads: (1) total QRS duration; (2) root mean-square-voltage in the terminal 40 ms (V40); and (3) low-amplitude terminal signal duration <40 μV. Based on prior work by other investigators[5,6,10] and in our laboratory (unpublished observations), a priori definitions of an abnormal SAECG included either a prolonged QRS >110 ms or the presence of a ventricular late potential (V40 <20 μV or low-amplitude signal duration [LAS] >38 ms). Because of the difficulty encountered when interpreting the SAECG in the presence of bundle branch block, these patients were excluded. All SAECGs were obtained while patients were not receiving antiarrhythmic drugs.[15]

Follow-up: Patients were enrolled between December 1986 and July 1988. All patients were followed by their primary physicians. Because the significance of the SAECG was not known at the time, the physicians were unaware of the results of the SAECG. Study end points were collected by review of patients' medical records, by communication with the patients' physicians or by telephone contact with the patients.

The following data were obtained regarding the patient's course after myocardial infarction: use of β-blocking and antiarrhythmic drugs; coronary artery bypass graft surgery; recurrent myocardial infarction; history of syncope; occurrence of documented sustained ventricular tachycardia or fibrillation; nonfatal cardiac arrest; and mortality. For patients who died during follow-up, attempts were made to obtain as many details as possible from witnesses and family, other hospitals, primary and other physicians, medical records and autopsy results. The mechanism of death was classified based on this available data without knowledge of the results of prior noninvasive tests. Each death was classified according to the criteria used in the Cardiac Arrhythmia Suppression Trial.[13] Sudden cardiac death was defined as death within 1 hour of onset of symptoms in a patient without evidence of ongoing ischemia, progressive heart failure or other serious medical illness, or for a patient who died in sleep. An arrhythmic end point was defined as sudden cardiac death, nonfatal cardiac arrest or documented sustained ventricular tachyarrhythmia.

Statistical methods: Comparisons between patients with and without abnormal SAECGs were performed by Fisher's exact test or chi-square analysis for discrete variables. The relations between arrhythmic end points and prognostic variables were assessed with the Kaplan-Meier product-limit estimate of the survival function[16] and tested with a log-rank test. The association of specialized test results (LV ejection fraction, ventricular arrhythmia on Holter, and SAECG) and the occurrence of arrhythmic end points during follow-up were analyzed using the Cox proportional hazards survival model,[17] and the multivariate association of significant univariate factors was analyzed with a stepwise Cox model. During follow-up, patient data was censored for the occurrence of nonsudden cardiac or noncardiac death, or if lost to follow-up.

A meta-analysis[18] was performed to ascertain with increased confidence the contribution of the SAECG to the risk of arrhythmic events after myocardial infarction when either the LV ejection fraction or Holter arrhythmia was available. Literature review of all studies that enrolled patients in a prospective manner and routinely obtained SAECGs and either LV ejection fractions or Holter recordings, or both, and in which long-term follow-up was available were selected. These studies were reviewed for their comparability using the following critical factors: timing of SAECG and noninvasive testing after myocardial infarction; SAECG technique; LV ejection fraction method; Holter definitions; duration of follow-up; and definition of end point(s).

TABLE I Characteristics of the Study Population (n = 182)

Variable	
History	
Age (yrs)	66 ± 13
Systemic hypertension (%)	61
Diabetes mellitus (%)	29
Smoking (%)	52
Prior myocardial infarction (%)	21
Anterior index myocardial infarction (%)	38
Peak creatine kinase (U/L)	871 ± 1124
LV function	
LV ejection fraction	0.44 ± 0.15
LV ejection fraction <0.40 (%)	41
LV ejection fraction <0.30 (%)	17
LV aneurysm (%)	13
Holter	
VPC/hr	32 ± 143
≥10 VPCs/hr (%)	19
Couplets/24 hrs	9 ± 51
≥1 couplet/24 hrs (%)	20
Ventricular tachycardia runs/24 hrs	0.6 ± 4.3
≥1 ventricular tachycardia run/24 hrs (%)	11
Abnormal Holter (%)	29
SAECG	
fQRS (ms)	104 ± 18
fQRS >110 ms (%)	27
V40 (μV)	44 ± 40
V40 <20 μV (%)	31
Low-amplitude signal duration (ms)	33 ± 15
Low-amplitude signal duration >38 ms(%)	26
Abnormal SAECG (%)	39
Treatment during follow-up	
β blockers (%)	45
Antiarrhythmic drugs (%)	12
Coronary bypass surgery (%)	13

fQRS = filtered QRS duration; LV = left ventricular; SAECG = signal-averaged electrocardiogram; V40 = voltage in terminal 40 ms; VPC = ventricular premature complex.

For each study, odds ratios were calculated with adjustment for low frequencies[19] when the patient samples were stratified according to presence or absence of LV ejection fraction <0.40 or of ventricular arrhythmia on Holter (as defined by each study). Each cell frequency was incremented by 0.5 to avoid zero frequency values. Pooled analyses were performed by combining log odds ratios using Woolf's method.[19]

RESULTS

Characteristics of study population: There were 226 patients who met the criteria for myocardial infarction. Of these patients, 22 would not be available for follow-up, because of geographic considerations, and thus were excluded from the study. An additional 22 patients were excluded from entry because of the presence of bundle branch block; this finding by the ECG makes the SAECG uninterpretable. Thus, 182 subjects met the eligibility criteria and gave informed consent.

LV ejection fraction was measured in 168 patients (by radionuclide methods in 136, by contrast angiography in 22, and by 2-dimensional echocardiography in 10). In 14 patients, LV ejection fraction was not available for technical or logistical reasons. A Holter recording was obtained in all 182 patients; there was recorder malfunction in 1 and repeat recording was not possible, yielding data on 181. All 182 patients had an SAECG.

TABLE II Relation Between Signal-Averaged Electrocardiographic Results and Myocardial Infarct Site, Left Ventricular Ejection Fraction and Holter Results

Variable	SAECG + (n = 71)	SAECG − (n = 111)	p Value
Site of myocardial infarct			NS
Anterior Q wave (n = 61)	17 (28%)	44 (72%)	
Inferior Q wave (n = 63)	28 (44%)	35 (56%)	
Non-Q wave (n = 35)	14 (40%)	21 (60%)	
Left ventricular function			NS
Left ventricular ejection fraction <0.40 (n = 68)	30 (44%)	38 (56%)	
Left ventricular ejection fraction ≥0.40 (n = 100)	37 (37%)	63 (63%)	
Significant ventricular arrhythmia by 24-hour electrocardiogram			NS
Present (n = 52)	24 (46%)	28 (54%)	
Absent (n = 129)	46 (36%)	83 (64%)	

NS = not significant; SAECG = signal-averaged electrocardiogram.

The characteristics of the 182 study patients are listed in Table I. The site of myocardial infarct was: anterior Q wave in 61 patients, inferior Q wave in 63, non-Q wave in 35, and indeterminate in 23. Only 15 patients received thrombolytic therapy.

Relations between signal-averaged electrocardiographic results and site of myocardial infarction, left ventricular ejection fraction and Holter recording: The frequency of an abnormal SAECG and its relation with preselected variables was examined (Table II). The site of myocardial infarction tended to be related to the prevalence of normal or abnormal SAECGs; however, the difference was not statistically significant. The odds ratio for having an abnormal SAECG in the presence of an inferior Q-wave myocardial infarction was 1.67, and in the presence of an anterior Q-wave myocardial infarction was 0.49.

The prevalence of depressed LV ejection fraction (<0.40) was 45% in the patients with an abnormal SAECG versus 38% in the patients with a normal SAECG. The prevalence of ventricular arrhythmia on the 24-hour Holter recording was 35% in patients with an abnormal SAECG compared with 25% in those with a normal SAECG. The odds ratio for an abnormal SAECG was a nonsignificant 1.33 for patients with an LV ejection fraction <0.40, and a nonsignificant 1.57 for those with ventricular arrhythmia on the 24-hour Holter recording.

There were no significant differences between patients with and without abnormal SAECGs for the following baseline clinical characteristics: age (66 ± 11 vs 66 ± 14 years); prior myocardial infarction (21 vs 13%); peak creatine kinase (750 ± 798 vs 945 ± 1285 U/L); LV aneurysm (7 vs 16%); β-blocker therapy (38 vs 49%); antiarrhythmic drug therapy (14 vs 11%); and coronary artery bypass graft surgery (16 vs 11%).

Therefore, the SAECG had only weak associations with an inferior site of myocardial infarction, an LV ejection fraction <0.40 and an abnormal Holter recording.

Arrhythmic end points during follow-up: The mean duration of follow-up was 14 ± 7 months (range 1 to

TABLE III Univariate Predictors of Arrhythmic Events

Variable	r	Chi-Square	Relative Risk	p Value
LVEF <0.40*	63	1.9	1.9	0.17
+ Holter	52	3.7	2.2	0.05
+ SAECG	71	5.7	2.7	0.017
fQRS >110 ms	49	8.4	3.0	0.004

*Statistically significant ($p < 0.05$) association with arrhythmic events when tested as a continuous variable.
fQRS = total filtered QRS duration; LVEF = left ventricular ejection fraction; SAECG = signal-averaged electrocardiogram.

32). There were 16 arrhythmic events during follow-up. Ten patients died suddenly, 4 had a documented episode of sustained ventricular tachycardia, and 2 were successfully resuscitated from cardiac arrest.

Risk factors for arrhythmic events: The Cox proportional hazards model was used to assess the risk of developing an arrhythmic event during follow-up in the presence of a predefined variable. According to our stated hypothesis, the presence of an abnormal SAECG was examined and was a significant ($p < 0.02$ by a log-rank test) univariate predictor of an arrhythmic event. Patients in whom the SAECG was abnormal had a 2.7-fold increase in risk for an arrhythmic event. Survival curves for the study group are shown in Figure 1. Survival without an arrhythmic event was significantly better in patients with a normal SAECG compared with that in patients with an abnormal result ($p < 0.05$). At the end of 1 year, 13% of the group with abnormal SAECGs had arrhythmic events; at the end of 18 months, the event rate reached 21%. In patients with normal SAECGs, the event rate was only 5% at 1 year, and 5% at 18 months.

The LV ejection fraction was significantly associated with the risk of an arrhythmic event when examined as a continuous variable ($p < 0.05$), and the risk was increased but not quite significantly when an LV ejection fraction cutoff of 0.40 was used (Table III). The presence of an abnormal Holter recording was associated with a borderline significant, increased risk of 2.15-fold for arrhythmic events (Table III).

These noninvasive predictors were assessed as to their independent contribution to increased risk using a stepwise procedure in the Cox model. The only variable that achieved statistical significance after adding ≥1 other variable was the presence of an abnormal SAECG.

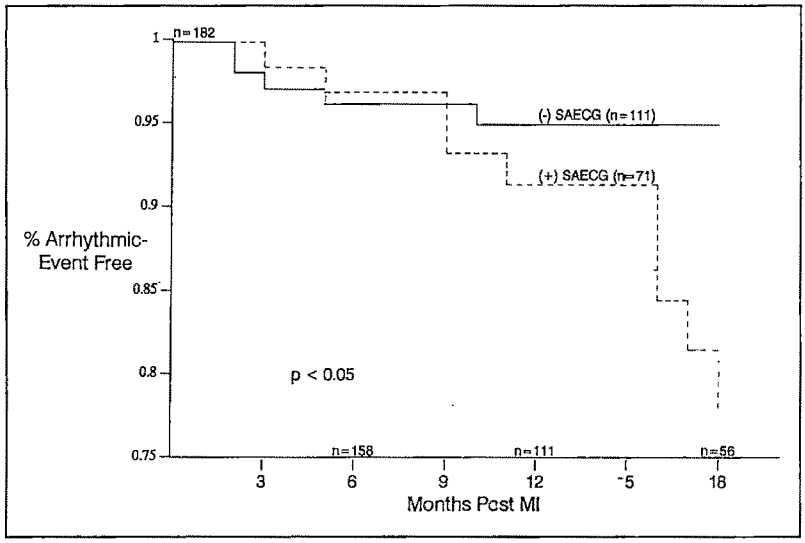


FIGURE 1. Kaplan-Meier survival plot of prediction of arrhythmic events after myocardial infarction (Post MI) by results of signal-averaged electrocardiogram (SAECG). Definitions of normal (−) and abnormal (+) test results are in text.

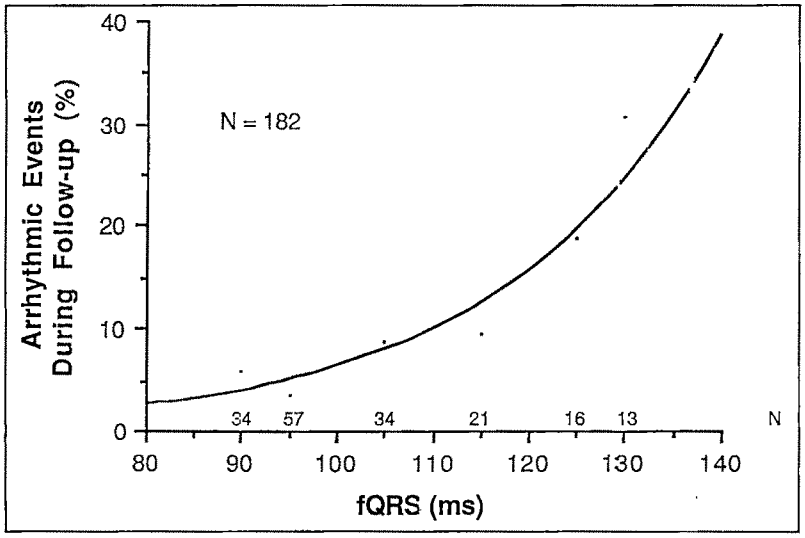


FIGURE 2. Relation of risk of arrhythmic events after myocardial infarction, and value of total filtered QRS duration (fQRS) from signal-averaged electrocardiogram.

The use of antiarrhythmic drugs was infrequent in this study. Because the SAECG can be altered by treatment with class I antiarrhythmic drugs,[15] all SAECGs were obtained when the patient was not taking antiarrhythmic medication. Subsequent treatment with antiarrhythmic drugs or β blockers, or revascularization by coronary bypass graft surgery, was not associated with the development of arrhythmic events by Cox analysis, although the power to detect these associations was low.

Signal-averaged electrocardiographic components as risk factors for arrhythmic events: Both V40 and LAS were not predictive of arrhythmic events (p = not significant [NS]) as univariate variables and were not independent of total filtered QRS duration (fQRS). However, fQRS was highly predictive; there was a threefold increased risk of an arrhythmic event in patients who had a prolonged fQRS on the SAECG (p = 0.004). As a continuous variable, fQRS conferred significant risk as well (p = 0.001). In Figure 2, the risk of an arrhythmic event is shown to be strongly related to fQRS. When fQRS was <100 ms, the risk of an arrhythmic event was ≤6%. As fQRS was prolonged, there was an increment in risk to the range of 9% for patients with durations of 100 to 120 ms. The risk increased to >10% when fQRS exceeded 120 ms. In patients with fQRS of 120 to 130 ms, the risk was 19%; in the small group of patients with fQRS >130 ms, the risk was 31% during follow-up.

Table III summarizes the results of the Cox proportional hazards model for all significant univariate predictors. The presence of a depressed LV ejection fraction or of ventricular arrhythmia on Holter ECG increased the risk of an arrhythmic event approximately twofold. An abnormal SAECG increased risk to an even greater extent; prolonged fQRS from the SAECG was the most potent risk factor imparting a threefold increase in the risk of an arrhythmic event.

Clinical use of noninvasive variables: We used the following 3 tests to predict risk of an arrhythmic event in the year after myocardial infarction: determination of LV ejection fraction; Holter recording; and SAECG. The performance of these tests, alone and in various combinations, is shown in Table IV. As a single test, the SAECG had the highest sensitivity predicting an arrhythmic event. The presence of either an abnormal SAECG or a reduced LV ejection fraction further improved the sensitivity of these tests, but the results were less specific. The finding of an abnormality on any 1 of the 3 tests identified all but 1 of the patients who experienced an arrhythmic event and was associated with the highest risk (5.8-fold). Conversely, a normal test result for all 3 tests identified a very low-risk group (high negative predictive accuracy). The presence of an abnormal SAECG and a reduced LV ejection fraction markedly enhanced the specificity of test results. The same was true for an abnormal SAECG and the presence of ventricular arrhythmia on Holter ECG. The risk of experiencing an arrhythmic event was greatest when the SAECG and the Holter, or the SAECG, the Holter

TABLE IV Clinical Value of Noninvasive Testing of Post–Myocardial Infarction Patients

Test	Sensitivity (%)	Specificity (%)	+ Predictive Accuracy (%)	− Predictive Accuracy (%)
LVEF <0.40	57	61	12	94
+ Holter	44	73	13	93
+ SAECG	69	62	15	95
LVEF <0.40 or + Holter	79	47	12	96
LVEF <0.40 or + SAECG	86	39	12	97
+ Holter or + SAECG	75	47	13	95
LVEF <0.40 or + Holter or + SAECG	93	31	11	98
LVEF <0.40 and + Holter	21	85	12	92
LVEF <0.40 and + SAECG	36	83	17	93
+ Holter and + SAECG	38	89	25	93
LVEF <0.40 and + Holter and + SAECG	21	94	25	93

LVEF = left ventricular ejection fraction; SAECG = signal-averaged electrocardiogram.

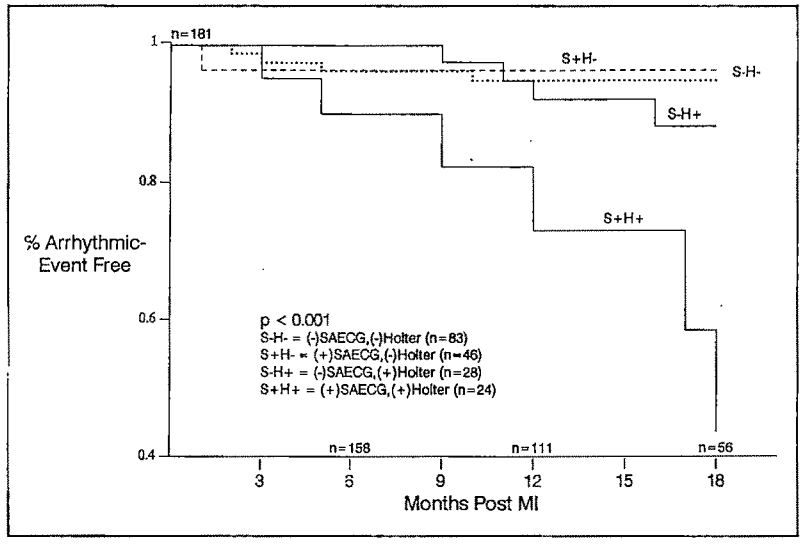


FIGURE 3. Kaplan-Meier survival plot of prediction of arrhythmic events after myocardial infarction (Post MI) by results of signal-averaged electrocardiogram (SAECG) and 24-hour Holter recording. Definitions of normal (−) and abnormal (+) test results are in text.

and the LV ejection fraction were abnormal. These combinations had a 25% positive predictive accuracy.

The combination of Holter recordings and SAECGs was very useful prognostically (Figure 3). The probability of having an arrhythmic event was significantly greater in patients with both an abnormal Holter and SAECG compared with those in whom only 1 test was abnormal or both were normal ($p < 0.001$). At 6 months, the actuarial incidence of arrhythmic events in patients with both an abnormal Holter and SAECG was 10% compared with 4% if both were normal. At 9 months, the event rates were 18 vs 4%, and at 12 months, 26 vs 4% in patients with both abnormal versus those with both normal Holter and SAECG, respectively. Thus, there was a progressively greater accumulation of events in patients with both abnormal Holter and SAECG, and a corresponding increasing disparity in events over time between those with both abnormal SAECG and Holter and those in whom both tests were normal.

Meta-analysis of signal-averaged electrocardiographic studies: Three studies (including the present study)[10,11] met the criteria for inclusion in the meta-analysis of SAECG when LV ejection fraction was known. The odds ratios for an arrhythmic event in the presence of an abnormal SAECG, stratifying for LV ejection fraction, is shown in Figure 4. When LV ejection fraction was depressed, the odds ratio ranged between 2.2 and 9.5, and when LV ejection fraction was ≥0.40, the odds ratio ranged between 3.3 and 10.7. The 6 specific odds ratios do not differ significantly from one another (chi-square = 2.35, degrees of freedom = 5; p = NS). Arrhythmic events were defined similarly in all 3 studies; the SAECG was obtained in a similar but

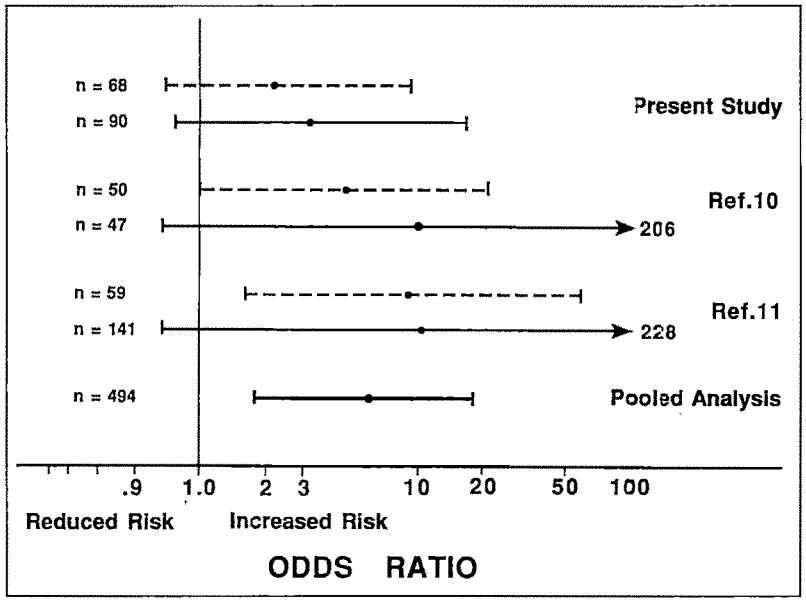


FIGURE 4. Odds ratios for risk of arrhythmic event when signal-averaged electrocardiogram was abnormal in 3 prospective studies with left ventricular ejection fraction stratified at 0.40. *Dashed lines* are left ventricular ejection fraction <0.40, *solid lines* are left ventricular ejection fraction ≥0.40, and *bold line* is pooled results. See text for complete discussion.

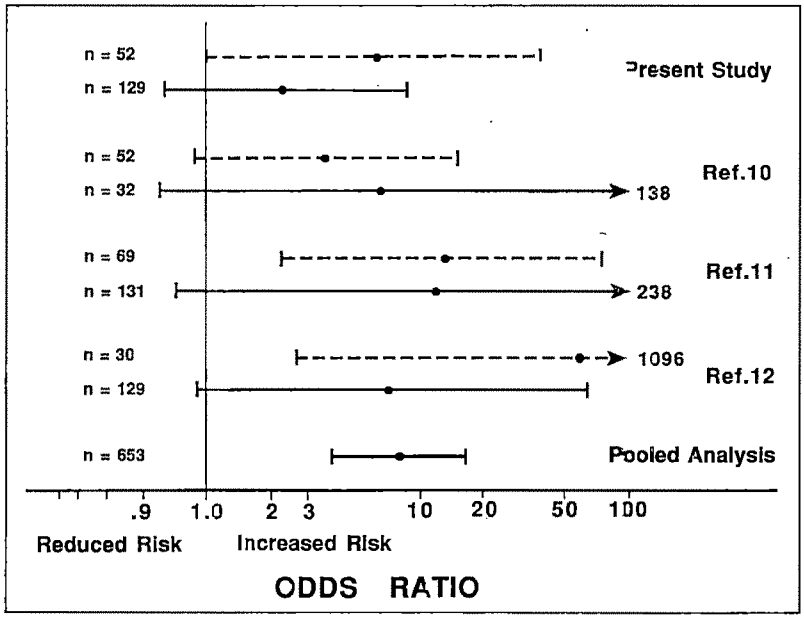


FIGURE 5. Odds ratios for risk of arrhythmic event when signal-averaged electrocardiogram was abnormal in 4 prospective studies with Holter results stratified according to presence/absence of significant ventricular arrhythmia. *Dashed lines* are significant ventricular arrhythmia on Holter, *solid lines* are no significant ventricular arrhythmia on Holter, and *bold line* is pooled results. See text for complete discussion.

not identical fashion in the 3 studies. The pooled results (Figure 4) show a significant increase in risk for an arrhythmic event when the SAECG was abnormal, independent of LV ejection fraction; the summary odds ratio was 6.0 with a 95% confidence interval of 1.9 to 18.5.

Four studies (including the present study)[10-12] met the criteria for inclusion in the meta-analysis when Holter results were known. The odds ratios for an arrhythmic event in the presence of an abnormal SAECG, stratifying for Holter results, is shown in Figure 5. When the Holter had frequent or complex ventricular ectopy, or both, the odds ratio ranged between 3.6 and 54.0, and when the Holter had no significant ventricular arrhythmia, the odds ratio ranged between 2.3 and 12.0. The 8 specific odds ratios do not differ from one another (chi-square = 5.59, degrees of freedom = 7; p = NS). Arrhythmic events were defined similarly in all 4 studies; the Holter results were analyzed and the SAECG was obtained in a similar but not identical fashion in the 4 studies. The pooled results (Figure 5) show a significant increase in risk for an arrhythmic event when the SAECG was abnormal independent of Holter results; the summary odds ratio was 8.1 with a 95% confidence interval of 3.9–16.6.

DISCUSSION

Use of the signal-averaged electrocardiogram after myocardial infarction: We have described the results of a prospective study of patients after myocardial infarction who underwent systematic noninvasive evaluation that included the SAECG, and were then followed and observed for the development of sustained ventricular arrhythmias or sudden cardiac death (presumed to be due to sustained ventricular tachycardia degenerating to ventricular fibrillation). It was our goal to determine if the SAECG predicted these arrhythmic events and if it did so independent of LV ejection fraction or ventricular arrhythmia on Holter monitoring, both known predictors of these end points.[2-4] Our analysis revealed that the SAECG: (1) identifies patients at risk of arrhythmic events; (2) predicts risk independent of other noninvasive data; and (3) can be combined with other noninvasive data to describe high- and low-risk groups.

The SAECG was strongly associated with an increased risk of sustained ventricular arrhythmia and sudden cardiac death during 14-month follow-up after hospital discharge. The risk for patients in whom a normal SAECG was recorded was very low during follow-up, whereas the risk was significantly greater for those with an abnormality on the SAECG. When an abnormal SAECG was recorded after myocardial infarction, the risk for a serious arrhythmic event increased 2.7-fold, an increment even greater than that imposed by a depressed LV ejection fraction or Holter ventricular arrhythmia. In patients with a normal SAECG after myocardial infarction, the risk of any arrhythmic event was no greater than 5% during follow-up. However, there was an increment in risk that progressively widened over time for patients with an abnormal SAECG. For patients with an abnormal SAECG, the risk was 13% at 1 year and increased to 21% at 18 months.

The SAECG is usually analyzed by measuring fQRS and also by computing the root-mean-square amplitude of the QRS signal in a terminal 40 ms segment (V40)[5] or determining the duration of the terminal portion of the summed vector QRS below a value of 40 μV (LAS).[6] When we examined these measurements individually, we discovered that only fQRS contributed singly or independently to the prognostic value of the SAECG. The terminal voltage and duration did not independently predict arrhythmic event risk. In fact, the SAECG became a more powerful tool if only fQRS were used to predict arrhythmic events. The arrhythmic event rate was strongly related to the degree of prolongation of fQRS (see Figure 2) and was greatly increased as fQRS became markedly abnormal (e.g., >120 ms). In previous studies,[10,11] V40 and LAS have been significantly different in patients with and without arrhythmic events; however, statistical comparisons were generally made without using survival models. In another study, Gomes et al[20] also found that fQRS was very strongly related to the development of sustained arrhythmias when tested with a Cox model. Why these terminal QRS measurements are not consistently useful is not clear; it may be that these values are highly sensitive to the signal-to-noise interface and that relatively small changes in the QRS offset markedly reduce their accuracy. In addition, the specifics of V40 and LAS do not have an electrophysiologic rationale and were developed in relatively small patient cohorts,[5,6] whereas fQRS may be a less arbitrary measurement that includes the late potential and conventional QRS.

Arrhythmic mortality is strongly related to the presence of LV dysfunction that can be estimated by measurement of the LV ejection fraction. For example, in the Multicenter Post-Infarction Program[2,21] involving >700 patients, there was a progressive increase in cardiac mortality as LV ejection fraction decreased, and an LV ejection fraction <0.40 conferred a 2.4-fold increase in risk of cardiac mortality at 1 year over an LV ejection fraction ≥0.40. Spontaneous ventricular arrhythmia can be detected on a 24-hour ECG, and the presence of either frequent or repetitive VPCs increased the risk of cardiac mortality in previous large studies. In the Multicenter Post-Infarction Program, the presence of ≥10 VPCs/hour was associated with an increase in 1-year cardiac mortality of 1.6-fold.[21] In the present study, these 2 well-established risk factors were both associated with increased risk of sustained ventricular arrhythmias and sudden cardiac mortality in patients after myocardial infarction; the relative risk of LV ejection fraction <0.40 was 1.9 and of ventricular arrhythmia on Holter was 2.2.

In previous studies that were performed in a prospective manner, the SAECG has been used successfully to predict sustained ventricular arrhythmias. Breithardt et al[8] showed that risk increased when a late potential was visually identified (4.3-fold) and that risk was greatest in those patients with the longest late poten-

tials. In a study using both the SAECG and programmed ventricular stimulation, Denniss et al[9] found that both cardiac death and sudden cardiac death were increased when the duration of the unfiltered averaged QRS was prolonged. For the occurrence of arrhythmic events, the risk was increased to a similar degree if a prolonged QRS was present or if ventricular tachycardia was induced by programmed stimulation. However, programmed stimulation and the SAECG did not predict the same group of patients with arrhythmic events.

Some previous reports[11,20] suggested that abnormal SAECGs were more likely at an inferior than anterior site of myocardial infarction and were more likely with LV dysfunction than normal LV function.[22] The present study trended in the same directions, but a strong association between site of myocardial infarction and the SAECG was not found. However, the absence of a strong association has important implications regarding use of the SAECG and suggests that the SAECG has the possibility of predicting outcome in patients after myocardial infarction independent of the presence of impaired LV function, a known and potent risk factor for sustained arrhythmias and sudden death.[2-4] Furthermore, abnormal SAECGs will not be severely weighted by patients with inferior myocardial infarction who may have lower risk for these events,[23,24] which could increase the number of false positive tests. The presence of either frequent or complex ventricular arrhythmia on the 24-hour ECG, another well-known risk factor,[2-4] was also not strongly associated with the SAECG. In fact, patients with abnormal SAECGs did not differ in any baseline characteristic from those with normal ones. However, inadequate statistical power may have contributed to these observations.

All 3 noninvasive tests predicted the occurrence of arrhythmic events in this study, but the SAECG had the strongest association. Other recent studies have also concluded that the SAECG was strongly associated with the subsequent development of sustained ventricular arrhythmias or sudden death in patients after myocardial infarction, with the SAECG independently related to these outcomes. Kuchar et al[11] found an abnormal SAECG present in 39% of 200 patients, and an arrhythmic event occurred in 17% of these versus only 1% of those with a normal SAECG. Similarly, Gomes et al[10] found an abnormal SAECG in 44% of 102 patients and noted that sustained ventricular arrhythmias occurred more frequently during follow-up in these than in those with a normal SAECG (29 vs 4%).

The most impressive use of the SAECG is its ability to predict very low risk when the results are normal. In the present study, the negative predictive accuracy was 95%, and the risk of an arrhythmic event was ≤5% by actuarial analysis. Other studies[8-12,25] had similar findings. Although the risk of an arrhythmic event with an abnormal SAECG is increased, the majority of these patients do not experience a fatal or life-threatening arrhythmia. This observation is partially related to short follow-up, but also raises the possibility that other factors need to be present in order for the reentry circuit to be activated. Lending credence to this hypothesis is our observation that the risk of sustained ventricular arrhythmia was markedly increased when the SAECG was abnormal, and the Holter recorded frequent or repetitive ventricular ectopic complexes, or both. Simplistically, the presence of both a trigger (VPC or ventricular tachycardia on Holter) and substrate (late potential on SAECG) may substantially augment the risk of a sustained arrhythmia compared with when either is present alone. Although the interaction between the results of multiple tests needs to be examined in larger studies, Cripps et al[12] had similar findings, and they interpreted their findings in a similar way.

A meta-analysis of all available prospective studies of the use of the SAECG after myocardial infarction was performed to enhance our confidence in the prognostic value of the SAECG relative to other noninvasive variables. In 3 studies that followed a total of 494 patients, the SAECG predicted a sixfold increase in risk of arrhythmic events independent of LV ejection fraction. In 4 studies that followed a total of 653 patients, the SAECG predicted an eightfold increase in risk of arrhythmic events independent of ventricular arrhythmia on Holter ECG. These are striking and important findings that corroborate our conclusions and emphasize the independent value of the SAECG as a prognostic tool.

Clinical implications: The SAECG is a noninvasive test that can rapidly and easily provide potent prognostic information regarding the risk of sustained ventricular arrhythmias and sudden cardiac death in patients after myocardial infarction. The SAECG, either alone or in conjunction with other noninvasive tests (Holter or LV function), can accurately stratify risk for a serious arrhythmic event. When the patient's risk is high, several recommendations can be made at the present time. Every effort should be made to use β blockers (if not clinically contraindicated), the patient may need more intensive or vigilant observation and care (especially for any warning symptoms such as dizziness and syncope), and thorough treatment of ischemia should be considered. Treatment with antiarrhythmic drugs is not indicated at the present time,[13] as the results of the Cardiac Arrhythmia Suppression Trial have clearly demonstrated. Electrophysiologic study to induce sustained ventricular tachycardia may be used to further stratify risk. Newer studies will undoubtedly use the SAECG to stratify for interventions such as the implantable cardioverter-defibrillator. Finally, in those patients with low risk as defined by the SAECG, interventions involving significant risk would be unwarranted.

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Technetium-99m Sestamibi Myocardial Imaging at Rest for Assessment of Myocardial Infarction and First-Pass Ejection Fraction

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The ability of technetium (Tc)-99m sestamibi myocardial perfusion imaging at rest to evaluate myocardial infarction and first-pass ejection fraction was studied in a trial involving 18 institutions. Protocol I compared regional perfusion with occurrence of infarction by Q wave or by gated blood pool scan wall motion abnormality in 146 patients. Protocol II assessed first-pass right and left ventricular ejection fraction in 85 patients. In protocol I, Tc-99m sestamibi images were abnormal in 104 of 111 patients (94%) with both a Q wave and a gated scan wall motion abnormality and was normal in 23 of 25 patients (92%) in whom both were normal. Therefore, concordance existed in 105 (94%) patients. Of 115 patients with a Q wave, 107 (93%) had an abnormal Tc-99m sestamibi study. Of 115 patients with a gated scan wall motion abnormality, 108 (94%) had an abnormal Tc-99m sestamibi study. Tc-99m sestamibi imaging showed corresponding perfusion abnormalities in 81% of 69 anterior Q-wave infarcts, 73% of 55 inferior Q-wave infarcts and 88% of 8 posterior infarcts. Specificity in normal regions on electrocardiography and wall motion was 91, 100 and 100%, respectively, for anterior, inferior and posterior regions, respectively, between wall motion and perfusion. Of 17 myocardial segments per patient, there was concordance in 74% of patients. First pass Tc-99m sestamibi imaging of ejection fraction agreed well with conventional first-pass imaging for the right and left ventricle. It is concluded that Tc-99m sestamibi myocardial imaging at rest reliably diagnoses and localizes infarction and assesses ejection fraction by first-pass imaging.

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Myocardial infarction occurs when a coronary artery occludes and severely interrupts coronary blood flow.[1] The traditional markers of infarction include Q waves on the electrocardiogram and an acute increase in serum myocardial enzymes.[2] Noninvasive evaluation of wall motion can define the infarct more precisely, but abnormal wall motion reflects a secondary consequence of the infarction.[3,4] Because the interruption in flow is the primary cause of the infarction, myocardial perfusion imaging has also been used in this setting.[5-8] At present, thallium-201 is the myocardial perfusion agent of choice.[9-11] Thallium-201 imaging usually shows a perfusion defect in regions of infarction, reflecting the coronary occlusion, and provides an assessment of the location and size of the infarction.[6]

Although thallium imaging has been widely applied for evaluating myocardial perfusion, it is limited by both a relatively low energy and long half life and the need for cyclotron production. The availability of technetium-99m hexakis 2-methoxy isobutyl isonitrile (Tc-99m sestamibi) as an alternative to thallium-201 for myocardial perfusion imaging represents a significant improvement in that Tc-99m has a higher energy of 140 KeV and shorter half-life of 6 hours.[12] The more favorable dosimetry resulting from the agent's physical and biological characteristics allows injections of 30 mCi/70 kg instead of 2 to 3.5 mCi for thallium-201. This results in a higher quality image due to a higher photon flux and less back scatter. Previous studies have demonstrated that Tc-99m sestamibi myocardial uptake is closely related to coronary blood flow and has a prolonged retention in the myocardium with little redistribution.[13-16] Because imaging is permitted several hours after injection, it appears to be an ideal agent for assessing acute myocardial infarction and for determining whether acute thrombolysis has successfully reestablished blood flow.[17-25] However, no improved sensitivity and specificity for detecting infarction has been shown compared with thallium-201.

Ejection fraction has been shown to have important prognostic value in coronary disease.[26,27] Previous studies have shown a relation between infarct size and ejection fraction.[28] Because a sufficiently high dose of Tc-99m is given, imaging of the initial passage of the tracer as a bolus through the heart and measurement of right and left ventricular ejection fraction using first-pass processing methods are feasible.[29,30] Therefore, assessment of first-pass ejection fraction could be a useful addition to the perfusion data, which cannot be provided with thallium perfusion imaging.

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*Institutions identified in Table I.

To test the usefulness of rest Tc-99m sestamibi imaging for these purposes, an 18-institution trial was initiated. In patients with known or suspected infarction, the presence and location of perfusion defects were compared with the presence and location of myocardial infarction as determined by the electrocardiogram and gated cardiac blood pool scan. A second group of patients was studied during the bolus injection of the tracer to determine whether accurate first-pass right and left ventricular ejection fraction could be obtained. The values were compared with conventional first-pass radionuclide ventriculography. The results show that this single agent detects and localizes myocardial infarction and determines first-pass ejection fraction.

METHODS

This study consisted of 2 protocols. Protocol I was performed in 17 institutions in the United States and Canada and assessed the ability of rest Tc-99m sestamibi (Cardiolite®) perfusion imaging to detect and localize myocardial infarction. Protocol II was performed in 4 institutions and assessed the ability of rest first-pass Tc-99m sestamibi imaging to measure right and left ventricular ejection fraction. The institutions and the principal investigators for both protocols are listed in Table I. This study was organized with the support of Dupont, Medical Products Department, North Billerica, Massachusetts, as part of phase III clinical testing of the Cardiolite kit for the preparation of Tc-99m sestamibi.

Protocol I methods — patient population: In all, 146 subjects were evaluated in protocol I. There were 24 normal subjects who had <1% likelihood of coronary heart disease and 122 patients with myocardial infarction based on definite clinical history, increase in creatine kinase or diagnostic electrocardiographic changes.[29] The myocardial infarction was considered "acute" if it was ≤14 days old or "previous" if it had been present for >14 days. Of the 122 infarct patients, 61 had previous infarctions, 50 had acute infarctions and 11 had both. Of the 61 with previous infarctions, 47 were >2 months old. There were 96 men and 26 women (age range 23–93 years, mean 61). The 24 normal patients included 9 men and 15 women aged 25 to 55 years (mean 33). All had a normal rest and exercise electrocardiogram and reached a minimum of 85% of the age-predicted maximal heart rate. None had a history of angina or myocardial infarction.

Technetium-99m sestamibi imaging methods: Tc-99m hexakis 2-methoxy isobutyl isonitrile was prepared by adding a mean of 65 mCi of sodium Tc-99m solution (range 21.3 to 85.0 mCi) to a Cardiolite kit. The kit was agitated gently and then placed in boiling water for 10 minutes. Labeling efficiency was tested before injection and found to be >90% in all cases.[22] The study consisted of an intravenous infusion of an average of 23 mCi of Tc-99m sestamibi (range 10 to 31 mCi) injected within 6 hours of preparation. Images were acquired within a mean of 125 minutes after injection (range 20 to 300 minutes). Planar images were acquired in the standard 3 projections (anterior, best septal left anterior oblique and left lateral). In addition, the patient had an electrocardiogram and a gated cardiac blood pool scan recorded with Tc-99m–labeled red blood cells within 48 hours.

TABLE I Institution Participation

Institution	Principal Investigator
Protocol I (n = 146)	
Massachusetts General Hospital	Charles Boucher, MD
Johns Hopkins Hospital	Lewis Becker, MD
Hotel Dieu de Montreal	Raymond Taillefer, MD
University of Alabama Hospitals (Birmingham)	Gerald Pohost, MD
Montreal Heart Institute	George Dupras, MD
Cedars-Sinai Medical Center	Daniel Berman, MD
Methodist Hospital (Houston)	Mario Verani, MD
St. Luke's Episcopal Hospital (Houston)	Warren Moore, MD
University of Iowa Hospitals and Clinics	Peter Kirchner, MD
St. Louis University Medical Center	Larry Samuels, MD
Yale University School of Medicine	Frans Wackers, MD
Brigham & Women's Hospital	B. Leonard Holman, MD
University of Virginia Hospital (Charlottesville)	George Beller, MD
Mayo Clinic	Manuel Brown, MD
Henry Ford Hospital	David Parkern, MD
University of Minnesota Hospital	Robert Boudreau, MD
Protocol II (n = 85)	
Harbor UCLA Medical Center	Ismael Mena, MD
Massachusetts General Hospital	Charles Boucher, MD
Duke University Medical Center	Robert Jones, MD
Yale University School of Medicine	Frans Wackers, MD
Methodist Hospital (Houston)	Mario Verani, MD

For the purposes of interpretation, the left ventricle was divided into 5 segments in each of the 3 projections. Anterior, inferior and posterior regions were analyzed separately. Any perfusion defect or wall motion abnormality in an apical segment was assigned to the territory of the adjacent abnormality if present.[20,21]

The perfusion images were all read without knowledge of clinical data by 2 experienced physicians, Drs. Wackers and Zaret at Yale University School of Medicine. All Tc-99m sestamibi images were scored segmentally as having either normal or reduced uptake. These core laboratory readings were compared with the analysis of the electrocardiogram and gated blood pool scan at each institution. The same segments on the gated blood pool scan were scored as normal wall motion, hypokinesia, and akinesia or dyskinesia. Of the 122 patients, 98 had 1 or more region of akinesia or dyskinesia and 17 others had 1 or more region of hypokinesia. Seven had no regional wall motion abnormalities. The electrocardiogram was read for Q waves in the inferior wall (leads II, III and F), anterior wall (precordial leads, leads I and L), or posterior leads (tall R waves in leads V_1 and V_2). A Q-wave infarction was present in 115 patients.

Protocol II methods: Sixty-six patients who already underwent a first-pass study with Tc-99m pertechnetate (n = 20) or Tc-99m diethylenetriaminepentaacetic acid (n = 46) underwent a repeat study with Tc-99m sestamibi prepared in the same way as protocol I. In addition, 19 clinically normal subjects were studied. The 45 studies at Harbor UCLA Hospital were performed using the standard software of the Elscint camera and the remaining studies at 3 other centers were obtained using

TABLE II Technetium-99m Sestamibi Imaging Versus Gated Blood Pool Scan Wall Motion in 122 Patients with Infarction

Gated Blood Pool Scan	Technetium-99m Sestamibi	
	Normal	Abnormal
Normal	3*	4
Abnormal	1	114*
Akinesia/dyskinesia only	1	97
Hypokinesia only	0	17

*Concordance = 117 of 122 (96%).

a Baird System 77 (Table I).[29,30] All had rapid sequence imaging acquired after a compact (<1 ml) bolus of Tc-99m sestamibi into an intravenous catheter in an antecubital vein. The dose injected averaged 20 mCi and ranged from 8 to 40 mCi.

Statistical analysis: Comparisons for continuous data were made using paired *t* test analysis. Incidence data were compared using chi-square analysis or Fisher's exact test. Sensitivity and specificity were determined for a Tc-99m sestamibi perfusion defect by comparing this to either or both a Q-wave by electrocardiogram or regional wall motion abnormality by gated blood pool scan on a patient, regional and segmental basis.

RESULTS

There were no severe adverse reactions to Tc-99m sestamibi. Many patients experienced a transient metallic taste immediately after the injection, but this completely disappeared within 1 to 2 minutes.

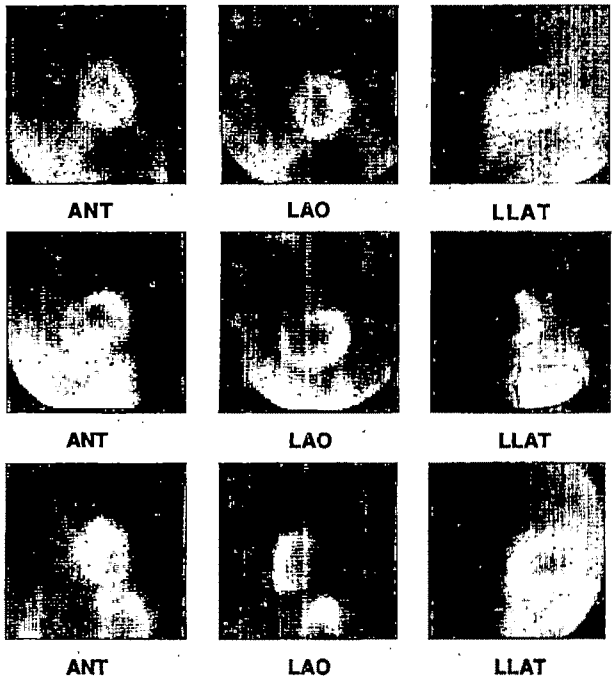


FIGURE 1. Three examples of technetium-99m sestamibi images in the 3 standard views: anterior (ANT), left anterior oblique (LAO) and left lateral (LLAT). *Top*, normal; *middle*, anterior myocardial infarction; *bottom*, posterior myocardial infarction.

Protocol I — myocardial infarction: Representative myocardial perfusion images in normal patients and patients with myocardial infarction are shown in Figure 1. In the infarct population of 122, 118 had a perfusion abnormality at rest by sestamibi imaging. There was a strong correlation between the presence of a perfusion defect and the presence of myocardial infarction as determined by both electrocardiogram and gated blood pool scan. Of 111 patients with both a Q wave and a scan wall motion abnormality, the Tc-99m sestamibi images were also abnormal in 104 (94%). There were 7 such patients who were not detected by Tc-99m sestamibi imaging. One patient with no Q wave and no wall motion abnormality was also normal by Tc-99m sestamibi imaging. This resulted in concordance in 105 (86%).

When the Tc-99m sestamibi images were compared with either electrocardiogram or gated blood pool scan alone, a similar close agreement was noted (Table II). Of 115 patients with an abnormal wall motion, 114 (99%) had an abnormal Tc-99m sestamibi study. In 3, both were normal. One patient with an abnormal gated scan had normal Tc-99m sestamibi studies, and 4 patients with normal gated scans had abnormal sestamibi studies. This resulted in concordance in 96%. Of 98 patients with 1 or more region of akinesia or dyskinesia by scan, 97 (99%) had a perfusion defect by Tc-99m sestamibi imaging. Of 17 patients with hypokinesia but no akinesia or dyskinesia, all had a perfusion defect. Of the 7 infarct patients with no wall motion abnormalities, 4 had perfusion defects.

Of 115 patients with myocardial infarction defined by electrocardiographic Q waves, 107 (93%) had detection by Tc-99m sestamibi imaging. Eight had Q waves by electrocardiogram with normal Tc-99m sestamibi imaging. Of 7 infarct patients without Q waves by electrocardiogram, 4 had abnormal and 3 had normal Tc-99m sestamibi imaging. This resulted in 90% concordance between Q wave and perfusion defect.

Specificity by patient was 92%. Of the 24 normal subjects, 22 (92%) had normal Tc-99m sestamibi images.

Regional analysis: The sensitivity and specificity of Tc-99m sestamibi imaging for an infarction by region is listed in Table III. Tc-99m sestamibi imaging was similarly sensitive in all infarct territories. A perfusion defect in the corresponding anatomic location was present in 81% of anterior wall Q-wave infarcts, 73% of inferior Q-wave infarcts and 38% of posterior infarcts. Tc-99m sestamibi imaging was abnormal in 73, 69 and 59% of patients with any anterior, inferior or posterior gated scan wall motion abnormality, respectively.

Specificity by region was defined as the incidence of normal Tc-99m sestamibi perfusion in infarction patients with regions that were normal by both electrocardiogram and gated blood pool scan. When a region was normal by electrocardiogram and gated blood pool scan, the Tc-99m sestamibi study was also normal in 77, 64 and 72% for the anterior, inferior and posterior regions, respectively. This resulted in an overall specificity of 71% (71 of 100 normal myocardial regions). Of 16 re-

TABLE III Analysis of Infarction by Region

Myocardial Perfusion Defect	Sensitivity vs ECG Q Wave	Sensitivity vs GBPS Regional Abnormality	Sensitivity vs Q Wave and Abnormal GBPS	Specificity vs Both Normal
Anterior	56/69 (81%)	69/95 (73%)	54/64 (84%)	17/22 (77%)
Inferior	40/55 (73%)	58/84 (69%)	36/46 (78%)	16/25 (64%)
Posterior	7/8 (88%)	39/66 (54%)	6/6 (100%)	38/53 (72%)

ECG = electrocardiographic; GBPS = gated blood pool scan.

TABLE IV Analysis by Myocardial Segment

Gated Blood Pool Scan	Technetium-99m Sestamibi Imaging		
	Normal	Abnormal	Total
Normal	910 (47%)	168 (9%)	1,078
Hypokinesia	275 (14%)	146 (8%)	421
Akinesia	155 (8%)	280 (14%)	435
Total	1,340	594	1,934

gions with Q waves without evidence of a wall motion abnormality in the same wall, 9 were normal on Tc-99m sestamibi imaging.

Segmental analysis: The correlation between Tc-99m sestamibi perfusion and gated blood pool scan regional wall motion by segment is shown in Table IV. There was concordance in 69% of segments. There were 430 (22%) abnormal myocardial segments by gated scan and normal by Tc-99m sestamibi, and 168 (9%) normal segments by gated scan and abnormal by Tc-99m sestamibi.

In the normal population, of the 24 patients evaluated, all had a normal electrocardiogram and gated scan. The specificity by segment was 99% for Tc-99m sestamibi imaging. There were 344 normal and 4 (1%) abnormal segments.

Protocol II — first-pass ejection fraction: The mean ± 1 standard deviation left ventricular ejection fraction in 66 protocol II patients was 47 ± 17% (ranging 11 to 86). This did not differ from the value obtained with the conventional Tc-99m first-pass imaging (48 ± 16%) (Figure 2). The right ventricular ejection fraction by first-pass Tc-99m sestamibi imaging (43 ± 11%, range 16 to 67) did not differ significantly from the corresponding value with conventional first-pass imaging (43 ± 10%) (Figure 3). In the 19 normal patients, mean left ventricular ejection fraction was 59 ± 5% and right ventricular ejection fraction was 45 ± 9%.

DISCUSSION

Infarct assessment: Tc-99m sestamibi myocardial perfusion abnormalities in 122 patients with a clinical diagnosis of myocardial infarction were compared to 2 gold standards: Q waves on the electrocardiogram, and abnormal wall motion by gated blood pool scan. Two standards were chosen because they were the 2 best markers of infarction available. Neither is perfect. The Q wave tends to be sensitive only for "transmural" infarctions and may not detect posterior, smaller or nontransmural infarctions. The gated blood pool scan may be too sensitive, with wall motion being abnormal in regions of severe ischemia without infarction. Small in-

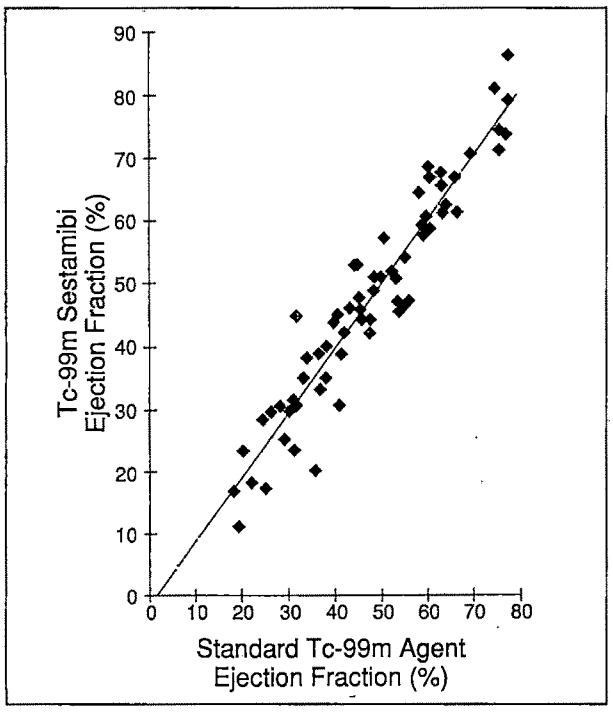


FIGURE 2. Linear plot of standard technetium (Tc)-99m first-pass left ventricular ejection (*abscissa*) and technetium-99m sestamibi left ventricular ejection fraction (*ordinate*). The correlation coefficient was 0.96, with equation y = 1.01(x) − 1.6.

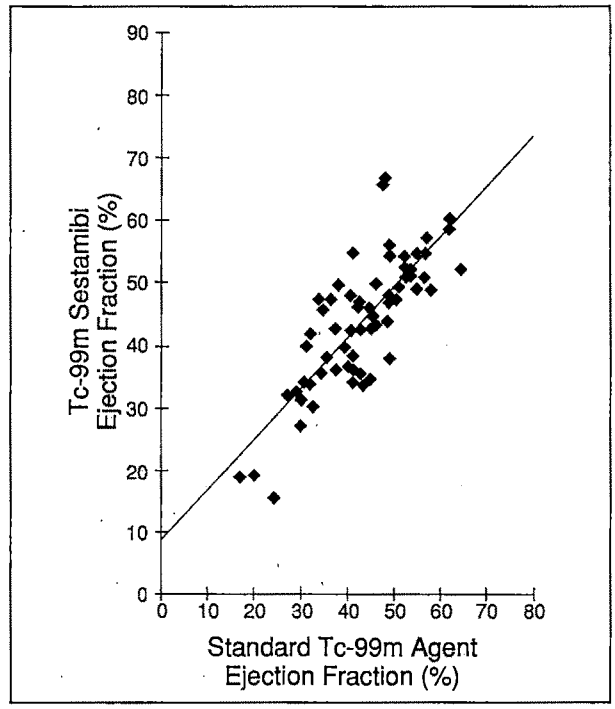


FIGURE 3. Linear plot of standard technetium (Tc)-99m first-pass right ventricular ejection fraction (*abscissa*) and technetium-99m sestamibi right ventricular ejection fraction (*ordinate*). The correlation coefficient was 0.79, with equation y = 0.81(x) + 8.6.

farcts can occur without any electrocardiogram or gated scan abnormalities. An echocardiogram may have a higher resolution, but it is not as easily compared to a planar perfusion study on a segment basis. A coronary angiogram would define the anatomic basis of the infarction, but this was not available for this study.

The results document a close correlation between Tc-99m sestamibi perfusion imaging and infarct presence and location as reflected on the electrocardiogram or gated blood pool scan. A perfusion defect was noted in 94% of patients with a Q-wave infarction and a regional wall motion abnormality. Perfusion was normal in 92% of 24 patients without infarction. Furthermore, the defects corresponded to the location of the Q wave in 81% of anterior, 73% of inferior and 88% of posterior infarcts. Similarly, these defects correspond to the location of a wall motion abnormality in 73% of anterior, 69% of inferior and 59% of posterior infarcts. Overall specificity was 71% (i.e., 71% of walls that had no Q waves and contracted normally had normal perfusion). Also, the images were considered by the investigators to be easy to interpret, having high resolution in comparison to thallium images. Because 115 of 122 patients with infarction had Q-wave infarcts, this high sensitivity may not apply to smaller non-Q-wave infarcts.

Although there was overall concordance in >90% of patients, there were individual, regional and segmental discordances in both sensitivity and specificity. This suggests no systematic underestimation or overestimation. It also suggests that some patients had concordant overall results due to abnormalities in apparently noncorresponding regions or segments. One explanation is that the gold standards are imperfect. Another is that similar regions could not always be compared in the same patient, because a perfusion study is very different from an electrocardiogram or gated scan. This is compounded by the fact that the region with the highest count density and thus most prominent activity on the Tc-99m sestamibi image represents normality, whereas the region with the highest count density and thus most prominent activity on the gated scan represents the worst abnormality. Because high count density regions are likely to dominate low count density regions, this may contribute to false-negative results, especially with smaller infarctions. In contrast, a perfusion defect at rest may represent underperfusion of a viable segment, which may contribute to some of the false-positive results. Finally, viewing the same part of the heart may be especially difficult with planar imaging in which truncated views of the heart are obtained. Tomographic imaging was not available.

First-pass ejection fraction assessment: The limited dose of thallium-201 administered for myocardial perfusion imaging does not provide sufficient counts for first-pass analysis. This is not a problem with Tc-99m sestamibi imaging, because 15 to 30 mCi are routinely used. The results in 85 patients demonstrate that this agent accurately measures first-pass right and left ventricular ejection fraction using suitable nuclear medicine computer systems. The correlation coefficient for left ventricular ejection fraction is 0.96, with that derived from conventional first-pass imaging. The correlation for right ventricular ejection fraction assessment is 0.79. This correlation is not as close as that of the left ventricle, and is likely related to greater technical problems such as (1) difficulty in separating right atrium from right ventricle, (2) the high background resulting from right atrial counts, and (3) the relatively few cardiac cycles associated with a bolus injection in an arm vein.

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A Comparison Between Lovastatin and Gemfibrozil in the Treatment of Primary Hypercholesterolemia

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A randomized, multicenter, double-blind, prospective, 18-week comparison of lovastatin with gemfibrozil was performed to compare their efficacy and tolerability in adults with types IIa and IIb primary hypercholesterolemia. Sixty men and 44 women aged 24 to 78 years participated in the trial. Each treatment group of 52 patients was closely matched by the randomization procedure. All participants met national cholesterol education program guidelines for evaluation and treatment. In all, 94 (90%) completed the 18 weeks of study.

After 18 weeks of diet-plus-active treatment, lovastatin decreased serum total cholesterol and low-density lipoprotein (LDL) cholesterol significantly better than gemfibrozil (adjusted mean decreases were 63 vs 35 mg/dl for total cholesterol and 67 vs 28 mg/dl for LDL; $p = 0.0001$). Gemfibrozil was more effective than lovastatin in increasing high-density lipoprotein (HDL) cholesterol (8 vs 5 mg/dl adjusted mean HDL cholesterol increases; $p = 0.0086$) after 18 weeks. No significant differences in the adjusted mean ratio of total to HDL cholesterol were noted, but the lovastatin group had a significantly greater adjusted mean reduction in the ratio of LDL to HDL cholesterol (1.8 vs 1.3; $p = 0.0013$). The gemfibrozil group achieved significantly greater reductions in very low density lipoprotein (VLDL) cholesterol and triglycerides compared with the lovastatin group (adjusted mean decreases were 14 vs 1 mg/dl for VLDL cholesterol and 71 vs 15 mg/dl for triglycerides). After 18 weeks of lovastatin therapy, 49% of patients achieved goal LDL cholesterol, whereas only 9% of those who took gemfibrozil achieved this goal ($p = 0.0001$).

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There has been renewed interest in blood lipids culminating in national guidelines for detecting and treating lipid abnormalities.[1,2] This has been stimulated by a convincing body of evidence that includes improved knowledge of the pathogenic mechanism,[3–5] the availability of a variety of generally well-tolerated pharmacologic agents that can improve the lipid profile,[6] epidemiologic evidence linking coronary disease incidence to blood lipids,[7–10] and controlled trial evidence demonstrating that treating blood lipids with diet and drugs reduces risk of atherosclerotic cardiovascular events[10–12] and slows progression of disease in human and nonhuman animals.[7,13–15]

Interest now focuses on when and how to treat persons with lipid abnormalities, rather than whether to treat. There is now a need to better define indications for and efficacy of the various agents available to treat lipid abnormalities. A multicenter, double-blind, 18-week study was conducted to compare the efficacy and tolerability of lovastatin and gemfibrozil in adult patients with primary hypercholesterolemia (types IIa and IIb). We report on the design and the results of that study.

METHODS

Study design: The study design was a randomized, double-blind, prospective comparison of lovastatin and gemfibrozil conducted in 7 centers. Initially, patients underwent 1 week of screening. On the first day of screening, a complete medical history was taken and a physical examination was performed. Laboratory studies included hematology, blood chemistry, serum lipid profile and urinalysis. Serum lipid values were confirmed by a second determination within a period of 1 week. Patients who had (1) total cholesterol levels ≥240 mg/dl or low-density lipoprotein (LDL) cholesterol levels ≥190 mg/dl, or (2) total cholesterol ≥240 mg/dl or LDL cholesterol ≥160 mg/dl and definite coronary artery disease or 2 other coronary artery disease risk factors (i.e. male gender, family history of premature coronary artery disease, cigarette smoking, hypertension, low levels of high-density lipoprotein (HDL) cholesterol, diabetes mellitus, and history of definite cerebrovascular or occlusive peripheral vascular disease), were entered into the diet-plus-placebo stage of the study. During this 6-week diet-plus-placebo period, all patients were given a standard cholesterol-reducing diet, lovastatin placebo (1 tablet once every evening) and gemfibrozil placebo (2 capsules twice daily).

At the end of 4 weeks and 6 weeks of the diet-plus-placebo period, each patient's serum lipid profile was evaluated. Based on these 2 evaluations, patients whose total cholesterol or LDL cholesterol values were still above the threshold levels of the entry criteria were enrolled in the 18 week diet-plus-active-treatment regimen and were stratified according to the following definitions: stratum 1 = patients with total serum cholesterol ≥240 mg/dl or LDL cholesterol ≥190 mg/dl who had neither definite coronary artery disease nor 2 other coronary artery disease risk factors; stratum 2 = patients with total serum cholesterol ≥240 mg/dl or LDL cholesterol ≥160 mg/dl who had definite coronary artery disease or 2 other coronary artery disease risk factors.

Within each stratum, patients were randomized in double-blind fashion to receive either lovastatin or gemfibrozil. Patients randomized to the lovastatin group received 1 lovastatin tablet (20 mg) once every evening and 2 placebo capsules twice daily (each capsule matching gemfibrozil 300 mg). Patients randomized to the gemfibrozil group received 2 gemfibrozil capsules (600 mg) twice daily and 1 placebo tablet once every evening (matching lovastatin 20 mg).

The dosage of gemfibrozil was constant throughout the 18 weeks of the study. The dosage for lovastatin could be increased. The goal of therapy was to achieve a serum LDL cholesterol of <160 mg/dl for patients in stratum 1 and a serum LDL cholesterol of <130 mg/dl for patients in stratum 2. This goal was used to determine if a dosage increase was appropriate. The LDL cholesterol values for the 6 and 12 weeks of therapy were reviewed and if the goal of therapy was not achieved, the lovastatin or matching placebo daily dosage in patients who were still receiving 20 mg/day was doubled for the remainder of the study. Maximum dosage of lovastatin could not exceed 40 mg/day. The design of study is shown in Figure 1.

Patients were evaluated immediately before the start of active treatment, and every 6 weeks throughout the active treatment period (weeks 6, 12 and 18). Evaluations included clinical assessment, serum lipid profile, serum chemistry panel, and the recording of any adverse effects. In addition, evaluations immediately before the start of the treatment and at the end of the study (week 18) included urinalysis, hematology, and an ophthalmologic (including slit-lamp) examination.

Patients: In all, 104 patients from 7 centers participated in the multicenter study. Those eligible for participation were men and women, aged ≥21 years, with primary hypercholesterolemia type IIa (LDL cholesterol elevation) and type IIb (LDL cholesterol and triglyceride elevation or very low density lipoprotein (VLDL) cholesterol elevation, or both), whose total and LDL cholesterol values were greater than the threshold levels of the entry criteria. Two patients whose total and LDL cholesterol values were below the threshold levels (total cholesterol 236 mg/dl in 1, and LDL cholesterol 159 mg/dl in the other) were still included in the study. Of

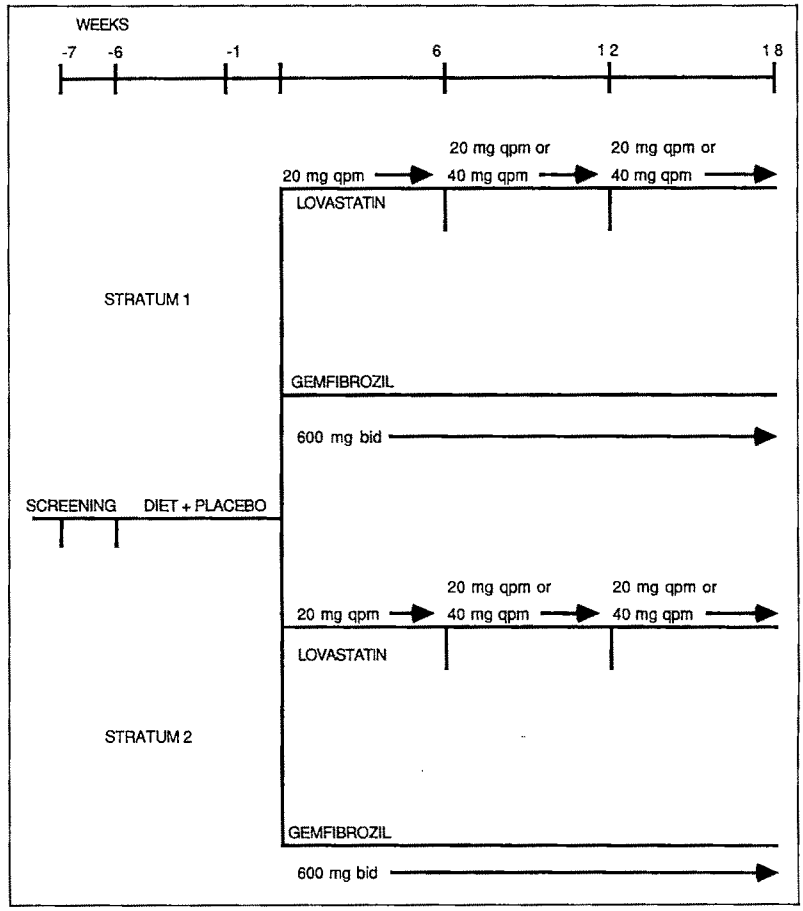


FIGURE 1. Design of study. bid = twice daily; qpm = evening meal.

TABLE I Coronary Artery Disease Risk Factors of Study Patients at Baseline (total sample size = 104)

	Gemfibrozil		Lovastatin		
	No of Pts.	%*	No. of Pts.	%	p Value†
Definite coronary artery disease	12	23	13	25	0.78
Hypertension	19	37	29	56	0.05
Family history of coronary artery disease	20	39	21	40	0.84
Cigarette smoking (>10/day)	9	17	3	6	0.07
Low HDL cholesterol (<30 mg/dl)	7	14	14	29	0.08
Diabetes mellitus	0	0	1	2	0.32
History of definite cerebrovascular or occlusive peripheral vascular disease	2	4	2	4	0.98

*In some cases percentages are computed using sample size of <104 because of missing values.
†p level for chi-square test.
HDL = high-density lipoprotein.

these patients, 1 was assigned to the lovastatin group and the other to the gemfibrozil group.

Patients were excluded if they were hypersensitive to any component of lovastatin or gemfibrozil, if dietary therapy was impractical or inadvisable, if they had a history of inability to adhere to a lipid-lowering diet or drug regimen, or both, or if they were premenopausal unless surgically sterilized (tubal ligation or hysterectomy). Patients who had any of the following conditions were also excluded: severe obesity (>30% overweight), active liver disease, severe renal dysfunction, preexisting gallbladder disease, untreated hypothyroidism and secondary hypercholesterolemia. Further exclusion criteria were mental and emotional disorders, substance abuse, any disease that could interfere with follow-up evaluations (e.g., malignancy), past or current therapy with immunosuppressive drugs, concurrent therapy with other lipid-lowering drugs or anticoagulants.

Laboratory methods: Total serum cholesterol was measured by the method described by Trinder[16] and Allain et al,[17] triglycerides by the procedure of Esders and Micheina,[18] and HDL cholesterol by the method described by Burstein et al.[19] All lipid analyses were performed by a central laboratory, SmithKline Bio-Science Laboratories, Van Nuys, California.

Statistical analysis: For baseline comparisons between the 2 treatment groups, the chi-square test (for incidence of coronary artery disease risk factors, and use of β blockers and diuretics) and the 2 independent sample t tests (for age and baseline lipids) were used.

The efficacy analyses were performed using an all patients treated approach. This approach incorporates data from all patients who have a baseline and at least 1 treatment observation. Cholesterol readings obtained during the week before randomization were used as baseline values. For 1 patient in the gemfibrozil group and 3 patients in the lovastatin group some of the data were missing at this week. Data from the preceding 2 weeks were used as baseline values for these patients. Thus, baseline values were all diet-plus-placebo observations. The lipid variables under consideration were total, LDL, HDL, the ratio of total to HDL, the ratio of LDL to HDL and VLDL cholesterol, and triglycerides.

Drug efficacy was assessed by analyzing changes from baseline observed after 6, 12 and 18 weeks of active treatment. Analyses are reported here on the 6- and 18-week data. Within each treatment group, the paired t test was used to test whether cholesterol levels after active treatment showed significant changes from baseline values. Between-treatment comparisons were performed using an analysis of covariance on the changes from baseline for the lipid variables, with treatment and center as class effects and the baseline values as a covariate. The center by treatment interaction effect was evaluated but was not found to be significant and was not used in any treatment comparison analyses. Similarly, to investigate the effects of the stratification, stratum class effect and strata by treatment interaction effect were tested. Neither were found to be significant and were not used in any treatment comparison analyses. Furthermore, analyses performed on the subset of subjects in stratum 2 (i.e., subjects with coronary artery disease or with 2 coronary artery disease risk factors) produced similar results as the total sample and therefore are not reported here. Stratum 1 did not have sufficient sample size for separate statistical tests, but all results were in the same direction as the full sample. Results are not reported here. The analysis of covariance technique was chosen because of its ability to consider the effects of baseline lipid values, center, stratum, treatment by stratum interaction and treatment by center interaction.

To control for multiple testing, multivariate analysis of variance with all lipid parameters was performed and Bonferroni adjustments were applied.

All tests were 2-tailed. The 0.05 level of significance was used in all cases for determining statistical significance.

RESULTS

Baseline characteristics: There were 104 patients enrolled in the study (30 in stratum I and 74 in stratum II), of whom 52 received gemfibrozil and 52 received lovastatin. Within each stratum patients were equally divided into the 2 treatment groups. There were 32 patients with type IIa and 20 patients with type IIb hyperlipidemia in each treatment group. The gender distribution was identical for the 2 treatment groups (42% women and 58% men). Mean age ± standard deviation was 56 ± 14 years for the gemfibrozil group and 54 ± 12 years for the lovastatin group (p = not significant, 0.65). The gemfibrozil group ranged in age from 24 to 78 years, the lovastatin group 28 to 78 years. There were no significant differences in serum lipid values at baseline between the 2 treatment groups. Mean total cholesterol was 293 mg/dl for those taking gemfibrozil and 284 mg/dl for those taking lovastatin (p = 0.41). The mean LDL cholesterol for gemfibrozil and lovastatin, respectively, was 212 and 209 mg/dl (p = 0.73), and the mean HDL cholesterol values were 45 and 44 mg/dl, respectively (p = 0.90). Mean ratios of the total

to HDL cholesterol for those taking gemfibrozil and lovastatin were 6.9 and 6.8, respectively ($p = 0.74$), and the mean ratio of LDL to HDL cholesterol was 5.0 for both treatment groups.

Table I contains baseline data on the incidence of major cardiovascular risk factors. The 2 treatment groups did not differ significantly with respect to incidence of definite coronary artery disease, definite cerebrovascular or occlusive peripheral vascular disease, diabetes mellitus, and family history of premature coronary artery disease. There were 3 significant or marginally significant differences. There were significantly more hypertensive subjects in the lovastatin group (29 or 56%) than in the gemfibrozil group (19 or 37%) ($p = 0.05$); the gemfibrozil group contained more cigarette smokers (9 or 17%) than the lovastatin group (3 or 6%) ($p = 0.07$). The lovastatin group had more patients with a history of low (<30 mg/dl) HDL cholesterol (14 or 29%) than the gemfibrozil group (7 or 14%) ($p = 0.08$). The 2 treatment groups did not differ significantly with respect to the proportion of patients receiving concurrent therapy with β blockers or diuretics.

Withdrawals: The number of patients who participated in the study at baseline and at week 6 was 104 (52 in each treatment group). The number of patients available at week 12 was 49 in the gemfibrozil and 52 in the lovastatin group. A total of 94 patients (90%) completed the 18 weeks of study, of whom 46 (49%) were in the gemfibrozil group and 48 (51%) were in the lovastatin group. The 10 patients who did not complete the study are discussed in the section on safety.

Titration: The dosage of gemfibrozil was constant for the 18 weeks at 1,200 mg/day. By the end of the study, 49% of the lovastatin group patients were receiving 20 mg/day and 51% were receiving 40 mg/day. Mean ± standard deviation of dosage for lovastatin was 30 ± 10 mg/day.

Efficacy results within treatment groups: Table II lists lipid values at baseline and changes in lipids at weeks 6 and 18 of diet-plus-active treatment. Data for all patients available for computation are included in Table II; sample sizes vary because lipid values for some of the patients were not available at all time points measured. Figure 2 shows percent changes from baseline for the 2 treatment groups at weeks 6 and 18.

After 6 weeks of diet-plus-active treatment, mean total cholesterol for patients in the gemfibrozil group decreased by 38 mg/dl (13%) to a mean of 254 mg/dl, mean LDL cholesterol was reduced by 28 mg/dl (13%) to a mean of 184 mg/dl, and mean HDL cholesterol increased by 5 mg/dl (11%) to a mean of 50 mg/dl. The mean of the ratio of total to HDL cholesterol was reduced by 22% to a mean of 5.4, and mean of the ratio of LDL to HDL cholesterol was reduced by 22% to a mean of 3.9. VLDL cholesterol and triglycerides were reduced by 15 mg/dl (44%) and 71 mg/dl (41%), respectively. All of these changes from baseline were highly significant ($p = 0.0001$).

For the lovastatin group, the mean total serum cholesterol was reduced by 55 mg/dl (19%) to a mean of 229 mg/dl, mean LDL cholesterol decreased by 57 mg/dl (28%) to a mean of 150 mg/dl, and mean HDL cholesterol increased by 3 mg/dl (7%) to a mean of 48 mg/dl. The means of the ratio of total to HDL cholesterol and the ratio of LDL to HDL cholesterol decreased to 5.1 (24%) and 3.3 (33%), respectively. All these changes from baseline were statistically significant ($p = 0.001$ for HDL cholesterol and $p = 0.0001$ for all others). The mean decreases in VLDL cholesterol (2 mg/dl) and triglycerides (15 mg/dl) in the lovastatin group were not statistically significant. Bonferroni adjustments for multiple testing did not affect significance. The improvements in lipids attained after 6 weeks of therapy were sustained over the full 18 weeks for both treatment groups.

TABLE II Cholesterol Data* by Active Treatment: Baseline, Weeks 6 and 18 Unadjusted and Adjusted Changes (adjusted for baseline and center)

	Gemfibrozil		Lovastatin		p Level†	
	Week 6	Week 18	Week 6	Week 18	Week 6	Week 18
Total cholesterol						
Baseline mean‡	293	293	284	285		
Mean decrease (unadjusted)	38§	37§	55§	62§		
Adjusted mean decrease	37	35	57	63	0.0047	0.0001
LDL						
Baseline mean	212	213	207	210		
Mean decrease (unadjusted)	28§	29§	57§	67§		
Adjusted mean decrease	28	28	58	67	0.0001	0.0001
HDL						
Baseline mean	45	46	45	45		
Mean decrease (unadjusted)	5§	8§	3§	5§		
Adjusted mean increase	6	8	3	5	0.08	0.0086
VLDL						
Baseline mean	34	34	32	30		
Mean decrease (unadjusted)	15§	15§	2	1		
Adjusted mean decrease	14	14	3	1	0.0001	0.0001
Triglycerides						
Baseline mean	172	167	164	161		
Mean decrease (unadjusted)	71§	74§	15	15		
Adjusted mean decrease	69	71	17	15	0.0001	0.0001
Total cholesterol/HDL ratio						
Baseline mean	6.9	6.8	6.8	6.7		
Mean decrease (unadjusted)	1.5§	1.8§	1.6§	1.9§		
Adjusted mean decrease	1.5	1.8	1.7	1.9	0.39	0.47
LDL/HDL ratio						
Baseline mean	5.0	5.0	4.9	4.9		
Mean decrease (unadjusted)	1.1§	1.4§	1.6§	1.8§		
Adjusted mean decrease	1.1	1.3	1.6	1.8	0.0012	0.0013

*Unit for all cholesterol variables is mg/dl.
†p level for treatment comparison adjusted for baseline and center.
‡Patients with missing values on a given week (weeks 6 or 18) are excluded from calculation of baseline mean for that week.
§Significant change from baseline (p level for paired t test ≤ 0.001)
HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; VLDL = very low density lipoprotein cholesterol.

Efficacy results between groups: Table II also lists, for each treatment group, 6- and 18-week mean changes adjusted for baseline and center. After 6 weeks of diet-plus-active treatment, lovastatin was significantly more effective than gemfibrozil in decreasing total serum and LDL cholesterol. The adjusted mean decrease in total cholesterol for the lovastatin group was 57 mg/dl, significantly higher than the 37 mg/dl decrease in the gemfibrozil group ($p = 0.0047$). Similarly, the adjusted mean reduction in LDL cholesterol for the lovastatin group (58 mg/dl) was significantly greater than that for the gemfibrozil group (28 mg/dl) ($p = 0.0001$). The differences between the groups were greater by the end of the study (week 18). The adjusted mean decrease in total cholesterol was 63 mg/dl for lovastatin and 35 mg/dl for gemfibrozil ($p = 0.0001$). The adjusted mean decrease in LDL cholesterol was 67 mg/dl for the lovastatin group and 28 mg/dl for the gemfibrozil group ($p = 0.0001$). Conversely, gemfibrozil was more effective than lovastatin in increasing HDL cholesterol. After 6 weeks of therapy, the adjusted mean increase in HDL cholesterol was 6 mg/dl for gemfibrozil and 3 mg/dl for lovastatin ($p = 0.08$). At week 18, the adjusted mean increase in HDL cholesterol for gemfibrozil (8 mg/dl) was significantly higher than that for lovastatin (5 mg/dl) ($p = 0.0086$).

TABLE III Patients Completing the Study by Goal Attainment at Week 18 (end of study)

	Goal LDL Attained*		Goal LDL Not Attained			
	No. of Pts.	%†	No. of Pts.	%	Total	
Gemfibrozil (n = 46)						
Stratum 1	1	7	13	93	14	
Stratum 2	3	9	29	91	32	
Lovastatin (n = 47)						
Stratum 1	9	64	5	36	14	
Stratum 2	14	42	19	58	33	
Total (n = 93)‡						
Gemfibrozil	4	9	42	91	46	p=0.0001§
Lovastatin	23	49	24	51	47	

*Goal LDL was < 160 mg/c for stratum 1 and < 130 for stratum 2.
†All percentages are row percentages.
‡Ten patients withdrew from the study by week 18 and 1 of the rema ning patients had missing LDL values.
§p level for chi-square test.
LDL = low-density lipoprotein cholesterol.

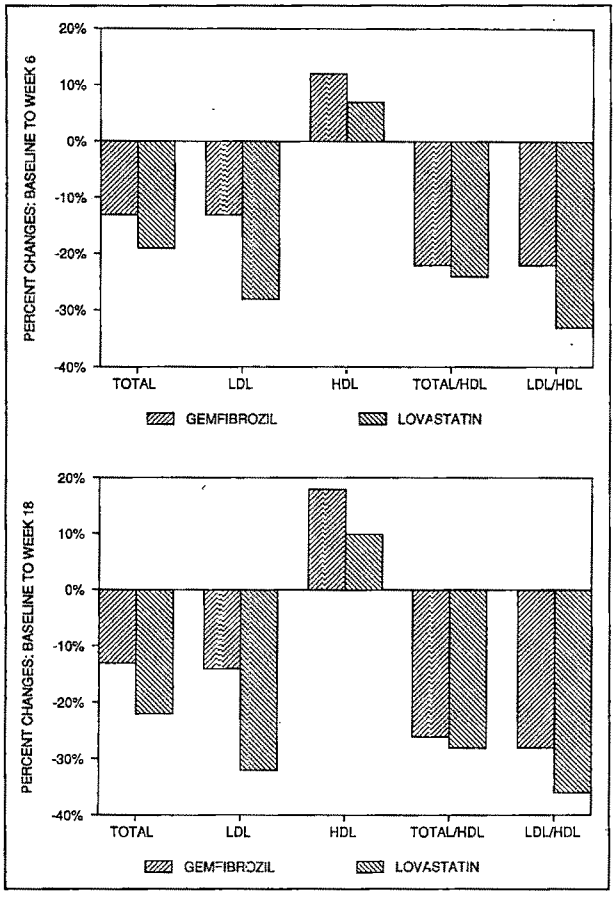


FIGURE 2. Percent changes from baseline for treatment groups. HDL = high-density lipoprotein; LDL = low-density lipoprotein.

There were no significant differences in the ratio of total to HDL cholesterol. The adjusted mean decreases for the lovastatin and gemfibrozil groups were, respectively, 1.7 and 1.5 at week 6 and 1.9 and 1.8 at week 18. The lovastatin group had significantly higher adjusted reductions of the LDL to HDL cholesterol ratio (1.6 for week 6 and 1.8 for week 18), compared with the gemfibrozil group (1.1 for week 6 and 1.3 for week 18) ($p < 0.0013$). Those taking gemfibrozil had significantly higher adjusted reductions in VLDL cholesterol (14 mg/dl for both weeks 6 and 18) compared with those taking lovastatin (3 mg/dl for week 6 and 1 mg/dl for week 18) ($p = 0.0001$). At week 6, the adjusted reduction in triglycerides was 69 mg/dl for the gemfibrozil group and 17 mg/dl for the lovastatin group ($p = 0.0001$); at week 18 the adjusted decrease was 71 mg/dl for the gemfibrozil group and 15 mg/dl for the lovastatin group ($p = 0.0001$). When the Bonferroni adjustment for multiple testing was applied, the only result changing in significance was HDL cholesterol at week 18. When adjusted for 7 lipid comparisons, its significance was marginal ($p = 0.06$).

Multivariate analysis of variance with changes from baseline for all lipid parameters as dependent variables confirmed the presence of an overall treatment effect in data at both weeks 6 and 18 ($p = 0.0001$).

Goal of low-density lipoprotein cholesterol achieved: Table III lists the percentage of patients in each stratum who achieved goal at week 18 (end of study). After 18 weeks of lovastatin therapy, 64% of patients in stratum 1 (9 of 14 patients) attained goal LDL cholesterol level (<160 mg/dl), whereas 42% of patients in stratum 2 (14 of 33 patients) achieved goal LDL cholesterol level (<130 mg/dl). After 18 weeks of therapy with gemfibrozil, only 7% of the patients in stratum 1 (1 of 14) attained goal LDL cholesterol level and only 9% of the patients in stratum 2 (3 of 32 patients) reached the goal LDL cholesterol of <130 mg/dl. Overall, 23 patients in the lovastatin group

(49%) achieved goal LDL cholesterol, whereas only 4 patients in the gemfibrozil group (9%) attained goal LDL cholesterol ($p = 0.0001$).

Adverse effects — safety evaluation: Of the 104 patients enrolled in the study, 10 (10%) withdrew over the 18-week period (6 patients from the gemfibrozil group and 4 patients from the lovastatin group). Of these, 4 patients, 3 in the gemfibrozil group and 1 in the lovastatin group, withdrew for reasons other than adverse experience (i.e., protocol violations, noncompliance, or lost to follow-up). Six patients, 3 in each treatment group, withdrew because of adverse experiences.

Overall, 55 patients (53%) had at least 1 clinical adverse experience during 18 weeks of therapy (i.e., reported on week 6, 12 or 18). Twenty nine of the 52 patients (56%) taking lovastatin and 26 of the 52 patients (50%) treated with gemfibrozil reported at least 1 clinical adverse experience. Most of these adverse experiences were mild and transient and were not determined to be causally related to the study drugs by the investigators. Table IV lists the categories of all clinical adverse experiences reported regardless of cause.

Of the 104 patients, 14 (13%) had at least 1 clinically nonsignificant laboratory value above the normal range during the 18 weeks of active treatment. Of these, 2 had values above the normal range on baseline examination, or had Paget's disease, thus explaining these abnormal values during the 18-week period of therapy. Of the remaining 12 patients, 6 were taking lovastatin and 6 gemfibrozil.

Only 2 patients, 1 in each treatment group, showed adverse changes from baseline on ophthalmologic examination. One patient taking gemfibrozil experienced a worsening of line changes (more spikes) in the left eye. One patient taking lovastatin experienced unspecified ophthalmologic changes deemed unrelated to drug therapy by the investigator.

TABLE IV Clinical Adverse Experiences Regardless of Cause*

	Gemfibrozil	Lovastatin
Gastrointestinal (gastric distress, diarrhea, nausea, flatus)	27	7
Musculoskeletal (muscle ache, joint pain, back pain)	13	14
Nervous system/psychiatric (headache, dizziness, lightheadedness)	4	17
Skin (facial flushing, hair loss)	6	3
Respiratory (bronchial pneumonia, rhinitis, sinusitis)	2	9
Special senses (blurred vision, dry eye syndrome)	0	7
Cardiovascular (myocardial infarction, angina, cardiac ischemia)	4	4
Genitourinary (decreased sexual drive, nocturia)	2	2
Miscellaneous (fever, flu, gout, tiredness, increased appetite, weakness)	5	8
Total	63	71

*Data in table correspond to number of times adverse experience category was reported over 18 weeks of treatment; some patients had > 1 adverse experience. Total number of patients with at least 1 clinical adverse experience during 18 weeks of therapy: gemfibrozil = 26, lovastatin = 29.

DISCUSSION

The results of this controlled trial are in accord with previously reported trials using these agents.[6,20,21] Gemfibrozil is known to be more efficacious in reducing elevated triglyceride levels and in raising the HDL cholesterol.[6,20] On the other hand, lovastatin has been found to be superior in reducing atherogenic LDL cholesterol. The 2 pharmaceutical agents studied by the criterion of the ratio of total to HDL cholesterol appear to have similar antiatherogenic potential; one by reducing the numerator of the ratio, the other by raising the denominator. However, by the criterion of the ratio of LDL to HDL cholesterol, lovastatin appears to have greater antiatherogenic potential. Irrespective of these criteria, using the national cholesterol education program guidelines that base treatment and goals on LDL cholesterol values,[2] lovastatin appears to be more efficacious.[21]

Both agents appear to be equally well tolerated and easily administered. What is not addressed in the trial is a possible difference in efficacy of each agent depending on the lipid profile at outset. It would appear likely from the available information that lovastatin would be most efficacious in persons with elevated serum total cholesterol because of a high LDL cholesterol component. Gemfibrozil would appear more likely to be efficacious in persons whose elevated cholesterol derives from a high triglyceride and VLDL cholesterol, accompanied by moderately elevated LDL and low HDL cholesterol.[6,20] The sample for this study does not contain enough patients with elevated triglyceride levels and VLDL cholesterol to test this hypothesis; thus, future controlled trials are needed.

APPENDIX

Participants: The study investigators: Henry R. Black, MD, School of Medicine, Yale University; William E. Cobb, MD, Division of Endocrinology, Department of Medicine, Brown University; Adrian Dobs, MD, School of Medicine, Johns Hopkins University; Harold D. Itskovitz, MD, New York Medical College; Joel Morganroth, MD, Hahnemann University; Richard C. Pasternak, MD, Cardiology Division, Beth Israel Hospital; Peter Schulman, MD, Cardiology Division, University of Connecticut.

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Blood Pressure, Plasma Atrial Natriuretic Peptide and Catecholamines During Rapid Ventricular Pacing and Effects of Beta-Adrenergic Blockade in Coronary Artery Disease

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To study neurohumoral control mechanisms of the hemodynamic response to ventricular tachycardia, arterial blood pressure, plasma atrial natriuretic peptide (ANP) and catecholamine levels were monitored during simulated ventricular tachycardia before and after administration of β blockade. Tachycardia was simulated by ventricular pacing at 150 beats/min for 150 seconds in 9 patients without and 14 with angiographically demonstrable coronary artery disease (CAD). The effects of intravenous propranolol (0.15 mg/kg) were evaluated in 7 control subjects and in 13 patients with CAD. Arterial blood pressure decreased to its minimum within 5 seconds after onset of pacing in all patients, the decrease being 27 and 30% (p = not significant) in the groups without and with CAD, respectively. Propranolol did not affect the initial decline, but blunted subsequent recovery. The ANP baseline levels were similar in both groups, increasing by 60% (p <0.05) and 71% (p <0.02) in the groups without and with CAD, respectively, during ventricular pacing. After administration of propranolol the increase in ANP was 180% in both groups. Rapid ventricular pacing did not affect catecholamine levels before propranolol, but after propranolol norepinephrine increased by 71 (p <0.02)and 97% (p <0.01) in patients without and with CAD, respectively. There was a significant correlation (r = 0.53, p = 0.001) between pacing-induced ANP and norepinephrine changes, but changes in arterial blood pressure did not correlate with those in either of these hormones. Thus, β-adrenergic blockade blunts blood pressure recovery during simulated ventricular tachycardia. However, this is partly counterbalanced by increased circulating norepinephrine levels. The positive correlation between ANP and norepinephrine changes shows that secretion of these hormones is interrelated. The lack of any correlation between hormonal changes and blood pressure changes suggests that other determinants of hemodynamic recovery, such as activation of neuroadrenergic system, exist under these circumstances.

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The hemodynamic consequences of ventricular tachycardia vary from a mild decrease in blood pressure to sustained hypotension, collapse and death. It has been suggested that the recovery of hemodynamics during ventricular tachycardia is determined by the rate of tachycardia,[1] incomplete filling and incoordinate contraction of the left ventricle,[2] atrioventricular asynchrony[3] and the autonomic nervous system.[4–6] Both supraventricular and ventricular tachyarrhythmias lead to increased plasma concentrations of atrial natriuretic peptide (ANP),[7–11] and it has been suggested that high plasma concentrations of this peptide may also contribute to the hypotension associated with ventricular tachycardia.[10] The present study was performed to assess the role of β-adrenergic stimulation, circulating catecholamines and ANP in the regulation of hemodynamic functions during simulated ventricular tachycardia, accomplished by rapid ventricular pacing. Two patients groups, one with and the other without documented coronary artery disease (CAD), were studied.

METHODS

Patients (Table I): The 23 patients, who had all been admitted to the hospital for coronary angiography, were divided into 2 groups on the basis of the following findings: 9 patients with normal coronary arteries (and most of them also atypical angina) and the remaining 14 documented CAD patients with typical effort angina. The CAD group had somewhat lower ejection fractions (obtained from quantitative left ventriculography), but the difference was not statistically significant. Beta-adrenergic blocking therapy was discontinued at least 2 days before angiography, but all other medication was allowed. The research was approved by the local ethical committee of the University Central Hospital, and all the patients gave informed consent.

Protocol: After left ventriculography and coronary angiography were performed, a quadripolar electrode catheter was introduced into the right ventricular apex through the femoral vein. At least 30 minutes after

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TABLE I Clinical Characteristics of the Study Groups

	With CAD (n = 14)	Without CAD (n = 9)
Age (years)	52 ± 2.5 (SEM)	51 ± 2.2 (SEM)
Men	11	3
Women	3	6
Symptoms		
NYHA		
I	1	0
II	7	1
III	5	1
IV	1	0
Atypical	0	7
Previous myocardial infarctions	10	0
No. of diseased coronary arteries (stenosed >50% of diameter)		
0	0	9
1	5	0
2	4	0
3	5	0
Left ventricular ejection fraction (%)	61 ± 3 (SEM)	70 ± 3 (SEM)*
Pacing-induced ischemia (pain and/or electrocardiographic changes)	7	0
Rapid ventricular pacing repeated after intravenous propranolol	13	7
Medication		
β-adrenergic blockers†	7	4
Calcium antagonists	8	6
Nitrates	11	8
Antiplatelet agents	7	2
Anticoagulants	1	0
Antiarrhythmics†	0	1
Digoxin and/or diuretics	2	3

*p = 0.053 compared with group with CAD.
†Withdrawn 48 hours before study.
CAD = coronary artery disease; NYHA = New York Heart Association; SEM = standard error of the mean.

completion of the angiography, the right ventricular apex was paced to a constant cycle length of 400 ms by stimuli of 2 ms duration at twice the diastolic threshold current. Preliminary tests showed that ventricular pacing of 2 to 3 minutes' duration was also well tolerated by patients with CAD experiencing chest pain. However, the hemodynamic recovery was usually complete within 2.5 minutes, and therefore this was chosen for the pacing period.

Systemic arterial pressure was monitored continuously from the femoral artery line. The average arterial pressure of 3 consecutive beats at indicated time points was taken to represent blood pressure at those times.

Surface electrocardiogram leads II, V_1 and V_5, ventricular local bipolar electrograms and intraarterial pressure were recorded simultaneously with a Mingograph 7 (Siemens-Elema) ink-jet recorder at a paper speed of 100 mm/s.

Blood was collected from the femoral artery to determine ANP and catecholamine concentrations. The first samples were obtained while the baseline recordings were being made, the second samples at the end of the pacing period, and the third samples 2 minutes after completion of the pacing.

After the first pacing period the patients were given intravenous propranolol at a dose of 0.15 mg/kg within a minimum time of 15 minutes, and the pacing and blood sampling procedures were repeated in 7 of 9 patients without and in 13 of 14 patients with CAD using an identical blood sampling schedule as before therapy with β blockade.

Atrial natriuretic peptide and catecholamine measurements: Blood samples for ANP assays were taken into tubes precooled on ice (containing ethylenediaminetetraacetate), centrifuged immediately, and the plasma stored at −20° C until assayed by radioimmunoassay as described previously.[12,13]

Norepinephrine and epinephrine were assayed as described by Taylor et al.[14] and modified by Turkka et al.[15]

Statistical analysis: An analysis of variance for repeated measurements was used to analyze time-dependent changes in blood pressure. To allow evaluation of the effect of β blockade on pacing-induced changes in blood pressures, the overall means of the blood pressure values during the pacing periods before and after β blockade were calculated as described by Matthews et al.[16] and compared by means of a subsequent paired *t* test. Blood pressure values at 5 and 30 seconds and at the end of the pacing period before and after β blockade were compared with the paired *t* test. The changes in ANP and catecholamines were tested using analysis of variance for repeated measurements followed by the paired *t* test when the concentrations at the end or after the pacing period were being compared with baseline values. Corresponding hormone levels in the 2 study groups were compared by means of the unpaired *t* test. The correlations between blood pressure, ANP and norepinephrine changes during ventricular pacing were evaluated by linear regression analysis. The results are expressed as means ± standard error of the mean and $p < 0.05$ was considered significant.

RESULTS

Blood pressure response (Figures 1 and 2): There was a rapid decrease in blood pressure after initiation of ventricular pacing in both groups; the maximal decrease in mean arterial blood pressure (27 and 30% in the groups without and with CAD, respectively) was observed at 5 seconds, after which blood pressure began to increase again, reaching the prepacing values at the end of the pacing period.

Acute β blockade with intravenous propranolol reduced the heart rate from 72 ± 6.3 to 62 ± 3.3 beats/min ($p < 0.05$) in the group without CAD and from 72 ± 3.9 to 62 ± 2.3 beats/min ($p < 0.01$) in the group with CAD, but it did not affect baseline blood pressures. Beta blockade did not affect the initial decline in blood pressure, although it did blunt the hemodynamic recovery. Systolic, diastolic and mean arterial blood pressures remained significantly reduced during ventricular pacing in the group with CAD after receiving propranolol ($p < 0.01$, systolic and mean arterial pressure;

p = 0.01, diastolic pressure), whereas the same was true only for systolic and mean arterial blood pressures in the group without CAD (p <0.01, systolic; p <0.02, mean arterial blood pressure; p = 0.07, diastolic blood pressure).

There was a rapid increase in systolic and a simultaneous decrease in diastolic pressures immediately after the pacing period in patients without CAD. The increase in systolic blood pressure was also seen in the other group, but the decrease in diastolic blood pressure was not so evident. Hemodynamic recovery was complete 2 minutes after pacing, leaving the blood pressures identical to those recorded before pacing in both groups.

Atrial natriuretic peptide levels (Table II): Baseline ANP levels were similar in both groups. The level of ANP then increased by 60% in the group without CAD (p <0.05) during ventricular pacing, and by 71% in the CAD group (p <0.02). After pacing it continued to increase in the CAD group, but decreased in the group without CAD. Beta blockade with propranolol did not affect baseline ANP levels, but the pacing-induced increase was higher, i.e., 180% in both study groups (p <0.01 in the group without CAD and p <0.02 in the CAD group). As before therapy with β-blockade, the hormone level continued to increase during the postpacing period in the CAD group, but not in the group without CAD.

Catecholamine levels (Table II): The epinephrine and norepinephrine levels were similar in both patient groups before therapy with β blockade, and were not affected by pacing. However, after β blockade, norepinephrine levels increased by 71% in the patients without CAD (p <0.02), and by 97% in patients with CAD (p <0.01). Epinephrine levels remained the same throughout in both patient groups also after β blockade.

Correlations between hemodynamic and hormone changes: Changes in ANP or norepinephrine levels during ventricular pacing were not correlated with the maximal decrease in mean arterial pressure—the 30-second value (blood pressure recovery phase) or the 150-second value (end of pacing)—but there was a significant correlation between the ANP level before pacing and the change in this hormone during pacing (p = 0.0006, r = 0.57), and between pacing-induced ANP

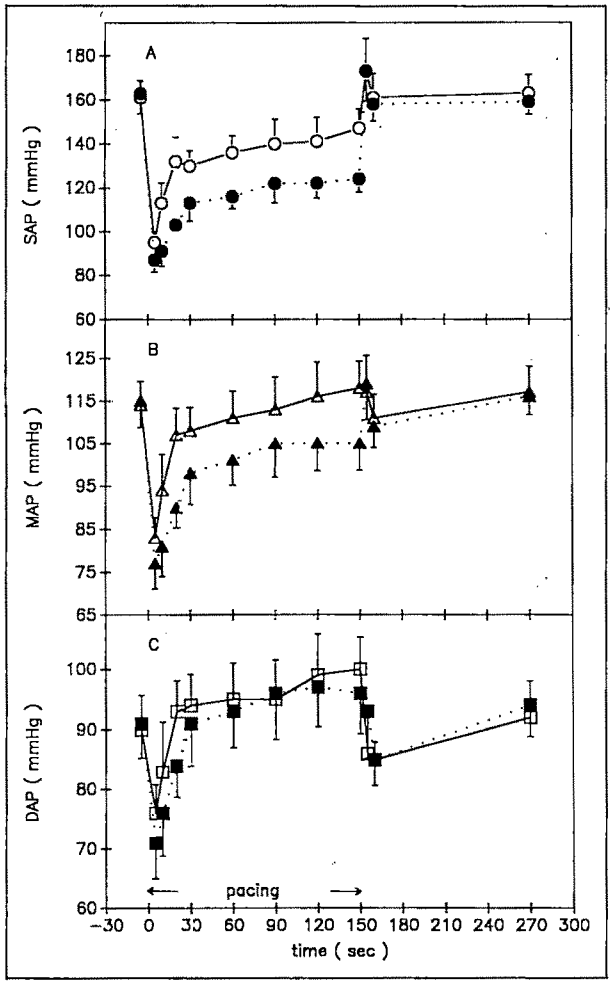


FIGURE 1. Blood pressure changes during rapid ventricular pacing in patients without coronary artery disease. Propranolol– versus propranolol+: p <0.01 for systolic (SAP), p <0.02 for mean (MAP), p = 0.07 for diastolic (DAP) arterial pressures. *Open symbols,* before β-adrenergic blockade; *closed symbols,* after β-adrenergic blockade.

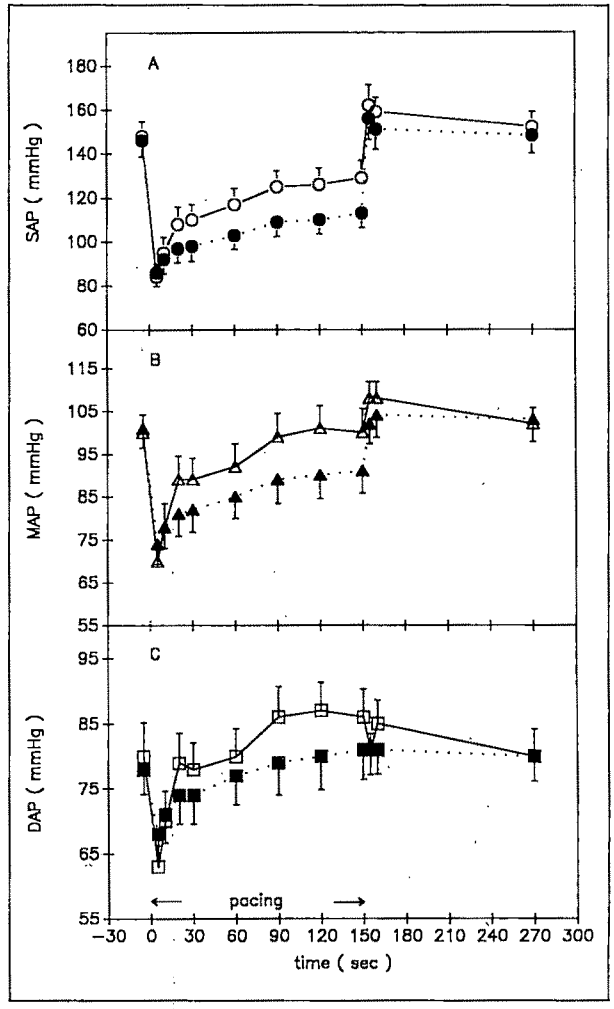


FIGURE 2. Blood pressure changes during rapid ventricular pacing in patients with coronary artery disease. Propranolol– versus propranolol+: p <0.01 for systolic (SAP) and mean (MAP) arterial pressures; p = 0.01 for diastolic (DAP) arterial pressure. Symbols as in Figure 1.

TABLE II Atrial Natriuretic Peptide and Catecholamine Levels During Ventricular Pacing

		With Coronary Artery Disease			Without Coronary Artery Disease		
	Propranolol	Prepacing	Pacing	Postpacing	Prepacing	Pacing	Postpacing
ANP	−	28 ± 6	48 ± 11*	64 ± 13†	30 ± 10	48 ± 10‡	39 ± 10
(pg/ml)	+	44 ± 9	125 ± 35*§	132 ± 40‡**	35 ± 8	97 ± 18†§	79 ± 22
Epinephrine	−	0.65 ± 0.17	0.52 ± 0.10	0.44 ± 0.10	0.46 ± 0.11	0.50 ± 0.10	0.49 ± 0.12
(nmol/liter)	+	0.88 ± 0.29	0.89 ± 0.26	0.56 ± 0.12*	0.51 ± 0.13	0.75 ± 0.14	0.70 ± 0.21
Norepinephrine	−	2.31 ± 0.51	2.54 ± 0.29	1.84 ± 0.29	2.41 ± 0.34	2.62 ± 0.36	2.56 ± 0.40
(nmol/liter)	+	1.78 ± 0.26	3.50 ± 0.47†**	2.16 ± 0.35	2.47 ± 0.38	4.22 ± 0.79*	3.26 ± 0.58‡**

‡,**p <0.05; *,§p <0.02; †p <0.01; *,‡compared with prepacing values with paired *t* test after analysis of variance; §,**compared with the corresponding values before β-adrenergic blockade.
Results are mean ± standard error of the mean.
Seven of 9 patients without and 13 of 14 with coronary artery disease were studied after administration of intravenous propranolol (0.15 mg/kg); p < 0.002 for ANP and norepinephrine in both study groups using analysis of variance for repeated measurements.
ANP = atrial natriuretic peptide.

and norepinephrine changes (p = 0.001, r = 0.53, Figure 3).

DISCUSSION

Mechanisms responsible for blood pressure changes: ANP increased after 2.5 minutes of ventricular pacing, and the increase was potentiated by β-adrenergic blockade in both patient groups. Although the hormone levels were not monitored in the course of pacing, it is unlikely that the observed changes would account for the rapid, initial blood pressure decrease. Moreover, the lacking correlations between changes in blood pressure and hormone levels indicate that ANP cannot be the main determinant of the hemodynamic recovery either.

Increased sympathetic nerve activity and regional adrenergic tone have been demonstrated during sustained ventricular tachycardia,[5,17] and this has also been suggested to be the primary mechanism responsible for hemodynamic recovery during ventricular pacing.[18,19] It has been reported that epinephrine or norepinephrine levels do not change during induced ventricular tachycardia.[20] In our study, norepinephrine increased only after propranolol administration. On the other hand, there was no correlation between pacing-induced changes in this hormone level and the maximal blood pressure decrease or recovery phase blood pressures, emphasizing the role of the sympathoadrenergic nervous system in hemodynamic recovery. Circulating norepinephrine may become more important, however, when left ventricular function is reduced or the β receptors of the heart are blocked. However, norepinephrine may play a specific role in counterbalancing the hypotensive action of ANP, whenever the levels of this hormone are increased.

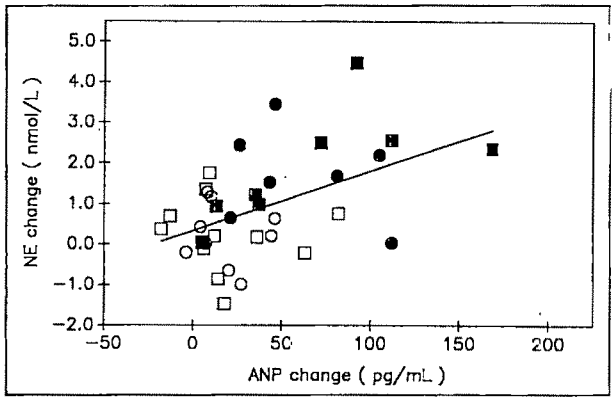


FIGURE 3. Correlation between atrial natriuretic peptide (ANP) and norepinephrine (NE) changes during rapid ventricular pacing. Patients without coronary artery disease (CAD) before propranolol *(open circles)*; patients without CAD after propranolol *(closed circles)*; patients with CAD before propranolol *(open squares)*; patients with CAD after propranolol *(closed squares)*.

Several other mechanisms have been proposed for the rapid decrease in blood pressures after initiation of ventricular tachycardia; these include immediate reduction in myocardial contraction and relaxation, ventriculoatrial regurgitation and ischemic myocardial dysfunction.[2,3,21] Left ventricular function and atrioventricular synchronization were not studied here, and their roles in the initial blood pressure decrease in our patients remain unknown. Before therapy with β-adrenergic blockade, the 2 groups demonstrated similar changes in blood pressure despite the fact that 50% of the patients with CAD developed ischemia in the course of pacing (Table I). Ischemia was therefore probably not responsible for blood pressure changes observed during pacing, but it may explain the postpacing differences in diastolic blood pressures between the groups (Figures 1 and 2).

Factors responsible for increased atrial natriuretic peptide secretion: The mechanisms by which ANP release takes place during ventricular tachycardia have remained controversial. It has been reported that atrioventricular valve regurgitation occurs,[22] leading to increased atrial pressure and stretch, and this has been suggested as the physiologic stimulus for ANP release.[23] However, a correlation between atrial pressure and hormone release during induced ventricular tachycardia has not always been found, and it has been speculated on other mechanisms, such as extracardiac origin or reduced clearance of peptide and atrial tachycardia due to ventriculoatrial conduction or ischemia.[10,24,25] Atrial pressure was not monitored in this study, but patients with CAD who experienced ischemia during pacing might have developed higher atrial pressures,[25] and this could explain the more sustained increase in ANP in this patient group. If this is the case, continuing pacing after 2.5 minutes may further increase ANP secretion.

In accordance with this, very high ANP concentrations have been detected in patients with ventricular tachycardia of long duration.[11] Because there were no differences in blood pressure recoveries between the 2 patient groups before β blockade, direct effects of ischemia on the release of ANP cannot be excluded.

Propranolol blunts hemodynamic recovery during pacing, leading to enhanced activation of arterial baroreflexes[26,27] and increases in regional adrenergic tone.[5] Furthermore norepinephrine and epinephrine have been reported to stimulate ANP release by increasing venous return or through direct α-adrenergic mechanisms on atrial myocytes.[28-30] ANP, however, inhibits catecholamine secretion and sympathoadrenal activity.[31-33] The correlation between norepinephrine and ANP changes during ventricular pacing in this study (Figure 3), and observed earlier during dynamic exercise,[34] would also fit the hypothesis that secretion of these hormones is counterbalanced. β-adrenoceptor blockade has been shown to potentiate exercise-induced release of ANP without affecting its plasma levels at rest, and this increase has been suggested to be due to the reduction in ventricular contractility.[35,36] However, there are no previous reports on the effects of β-adrenoceptor blockade on the levels of ANP during ventricular tachycardia in humans.

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Physiologic Responses to Recumbent Versus Upright Cycle Ergometry, and Implications for Exercise Prescription in Patients with Coronary Artery Disease

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To clarify the influence of body position on exercise prescription, 14 men (mean age ± standard deviation 60.0 ± 6.1 years) with coronary artery disease who underwent randomized recumbent and upright cycle ergometer tests to volitional fatigue were studied. At 100 watts, heart rate (HR), systolic blood pressure, oxygen consumption ($\dot{V}O_2$), rate pressure product and rating of perceived exertion were greater ($p < 0.05$) in the upright than in the recumbent position. At peak exercise, however, these variables were not significantly different. Regressions of relative HR versus $\dot{V}O_2$ for recumbent and upright cycle ergometry were comparable: $y = 1.24x - 32.7$ and $y = 1.26x - 31.5$, respectively, where y = % maximal $\dot{V}O_2$, and x = % maximal HR. These findings indicate that recumbent exercise prescriptions may be based on the peak HR and $\dot{V}O_2$ values obtained during upright cycle ergometry, and vice versa. However, differences in the cardiorespiratory responses at submaximal exercise preclude the interchangeability of upright and recumbent training work rates.

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Previous studies showed that cardiorespiratory responses to exercise may vary from the upright to the supine position.[1,2] Because the recumbent position is intermediate to these it is important to clarify the effects that it may have on exercise performance. Moreover, appropriate guidelines are needed for prescribing exercise in the recumbent position, particularly when baseline studies are conducted using upright ergometry. The purposes of this investigation were to compare the cardiorespiratory and perceptual responses of low-risk cardiac rehabilitation patients to upright and recumbent exercise, and to clarify the effect of body position on the exercise prescription.

METHODS

Subjects: Our study group consisted of 14 men with documented coronary artery disease. Their physical characteristics, clinical status and medications are listed in Table I. Patients met the following criteria: negative symptom-limited exercise test with oxygen consumption ($\dot{V}O_2$) within the preceding 12 months; normal exercise hemodynamics; aerobic capacity of ≥5 METs (1 MET = 3.5 ml/kg/min); absence of serious ventricular arrhythmias; ejection fraction >40%; and participation in cardiac rehabilitation for ≥4 months, exercising at 60 to 80% of maximal $\dot{V}O_2$ ($\dot{V}O_2$max).

Exercise testing: After procurement of signed, informed consent, each patient performed randomly assigned recumbent and upright progressive exercise tests within 1 week of each other at a similar time of day. Tests for upright work were conducted on a standard EC-3000 Cateye Ergociser and for recumbent work on a modified version of that device (Figure 1); thus, both ergometers had identical control consoles and eddy current resistance systems.

The protocol for the ergometer tests included a 2-minute initial power output (warm-up) with the subject exercising at 25 watts (1 watt = 6.12 kg-m/min), using a pedaling rate of 50 revolutions/minute. Thereafter, the power output was increased in stages by 25 watts every 2 minutes until volitional fatigue (i.e., the work rate at which the designated pedal speed could no longer be maintained) or the power output at which significant clinical signs or symptoms (i.e., chest pain, significant ST-segment depression or serious ventricular arrhythmias) developed. For comparative purposes, a

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standard submaximal power output (100 watts) was designated.

Respiratory variables, heart rate (HR), blood pressure (standard cuff method) and perceived exertion were determined at each power output and at peak effort. Expired gas was collected and analyzed on-line every minute. The electrocardiogram was monitored continuously by oscilloscope, with 3-channel (V_1, V_5, and aVF) recordings obtained throughout the exercise test, and 12-lead electrocardiograms recorded at the end of each stage and during maximal exercise. Perception of the intensity of physical effort at submaximal and maximal exercise was obtained using the Borg (6 to 20) scale.[3] Equipment enjoyment was assessed after each test by the 11-point Feeling scale (+5 = very good; +3 = good; +1 = slightly good; 0 = neutral; −1 = slightly bad; −3 = bad; −5 = very bad).[4]

Metabolic data were obtained by the Medical Graphics CAD/Net System 2001. The system includes a computer assembly for on-line 60-second calculations of $\dot{V}O_2$ (ml/kg/min), minute ventilation, carbon dioxide production ($\dot{V}CO_2$) and respiratory exchange ratio ($\dot{V}CO_2 / \dot{V}O_2$). Before each test, the pneumotachometer was referenced with a 3-liter syringe, and the gas analyzers were calibrated with room air and a certified oxygen/carbon dioxide concentration.

Electrocardiogram and HR determinations were obtained using the Quinton 5000 Computer Assisted System for exercise. The electrocardiogram was calibrated to 1 mV/10 mm deflection before each test.

Statistics: Data were compared using the paired *t* test. A p value <0.05 was considered statistically significant. Values are expressed as mean ± standard error. Relations between relative $\dot{V}O_2$ (expressed as % $\dot{V}O_2$max) and HR (expressed as % HRmax) were subjected to trend analyses using the linear regression techniques outlined by Steel and Torrie.[5] Upright and recumbent regressions (slopes and intercepts) of % $\dot{V}O_2$max on % HRmax were tested for equality by the large sample Z test and the multiple regression dummy variable model.

RESULTS

All 14 subjects completed the recumbent and upright ergometer protocols without demonstrating significant ST-segment depression (≥1.0 mm horizontal or downsloping), serious ventricular arrhythmias, or abnormal blood pressure responses or symptoms.

Maximal exercise responses to recumbent and upright cycle ergometry are listed in Table II. The validity of these data is reflected by a respiratory exchange ratio above unity, the attainment of 88 to 91% of age-predicted maximal HR, and a high rating of perceived exertion (very hard to very, very hard). Peak power output (watts) and exercise time (minutes) were significantly greater ($p < 0.001$) during recumbent cycle ergometer testing, whereas the remaining variables were not significantly different.

Cardiorespiratory and perceptual responses to recumbent and upright cycle ergometry at a standard

TABLE I Subject Characteristics (n = 14)

	No.
Physical characteristics*	
Age (yrs)	60 ± 6
Height (cm)	177 ± 5
Weight (kg)	85 ± 11
Clinical status	
Myocardial infarction	1
Bypass surgery	2
Myocardial infarction/angioplasty	3
Myocardial infarction/bypass surgery	6
Myocardial infarction/angioplasty/bypass surgery	2
Medications	
β-adrenergic blockers	4
Digitalis glycosides	1
Antiarrhythmics	2
Nitrates	4
Calcium antagonists	8
Antihyperlipidemic agents	4
Antiplatelets	12

*Values are expressed as mean ± standard deviation.

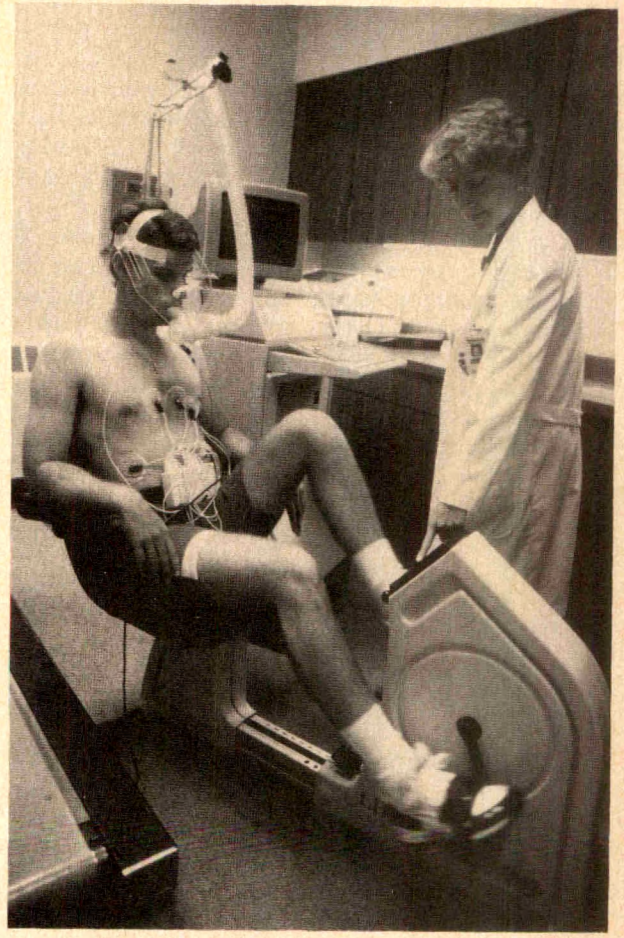


FIGURE 1. LIFEPlus 2000 cycle ergometer as used for recumbent exercise. A slightly reclining seat position distributes body weight evenly over the buttocks and lower back. Mean angle (± standard error) of horizontal line extending from hip relative to trunk was 115 ± 1.2° in recumbent position. Individual seat adjustments were made to insure slight bend at knee (≅ 5°) at maximal leg extension.

TABLE II Comparison of Maximal Exercise Responses to Recumbent and Upright Cycle Ergometry*

	Recumbent	Upright	p Value
Oxygen consumption (ml/kg/min)	22.7 ± 1.5	22.6 ± 1.6	NS
Heart rate (beats/min)	141 ± 3	145 ± 5	NS
Oxygen pulse (ml/beat)	14.0 ± 0.9	13.5 ± 0.9	NS
Ratings of perceived exertion	17.9 ± 0.3	17.7 ± 0.3	NS
Ratings on Feeling scale	+3.7 ± 0.3	+2.9 ± 0.4	NS
Systolic blood pressure (mm Hg)	202 ± 6	204 ± 4	NS
Diastolic blood pressure (mm Hg)	90 ± 4	91.6 ± 3	NS
Rate pressure product (mm Hg × beats/min × 10^{-2})	285 ± 12	297 ± 12	NS
Power output (W)†	177 ± 7	154 ± 5	0.001
Exercise time (min)	13.8 ± 0.5	11.8 ± 0.4	0.001
Respiratory exchange ratio	1.2 ± 0.03	1.3 ± 0.03	NS
Minute ventilation (liters/min)	89 ± 6	96 ± 7	NS

*Values are expressed as mean ± standard error; †1 W = 6.12 kg·m/min^{-1}.
NS = not significant.

TABLE III Comparison of Submaximal Exercise Responses to Recumbent and Upright Cycle Ergometry*

	Recumbent	Upright	p Value
Oxygen consumption (ml/kg/min)	13.6 ± 0.6	16.0 ± 0.9	0.001
Heart rate (beats/min)	104 ± 4	115 ± 4	0.001
Oxygen pulse (ml/beat)	11.5 ± 0.7	12.0 ± 0.6	NS
Ratings of perceived exertion	10.7 ± 0.7	11.7 ± 0.7	0.001
Systolic blood pressure (mm Hg)	170 ± 5	183 ± 5	0.01
Diastolic blood pressure (mm Hg)	79 ± 4	87 ± 3	0.01
Rate pressure product (mm Hg × beats/min × 10^{-2})	177 ± 8	212 ± 11	0.001

*Standard submaximal work rate = 100 W; values expressed as mean ± standard error.
NS = not significant.

submaximal power output (100 watts) are listed in Table III. Relative $\dot{V}O_2$, HR, rating of perceived exertion, systolic and diastolic blood pressures, and rate pressure product were significantly greater ($p < 0.01$) in the upright position. In contrast, no significant difference in oxygen pulse was observed.

Regression equations relating % $\dot{V}O_2$max to % HRmax were calculated using the $\dot{V}O_2$ and HR values (≥4 data points per patient) obtained during progressive power outputs. The recumbent (Rec) and upright (Upr) % $\dot{V}O_2$max (y) on % HRmax (x) regression equations including the standard errors for the slope and intercept terms, correlation coefficients (r), and standard errors of estimate (SEE; % $\dot{V}O_2$max) were: $y_{(Rec)} = 1.24\ (\pm 0.11)x - 32.7\ (\pm 7.7)$ ($r = 0.80$; SEE = 13.6); and $y_{(Upr)} = 1.26\ (\pm 0.09)x - 31.5\ (\pm 6.6)$ ($r = 0.87$; SEE = 11.3). Both the large sample Z test and the dummy variable model revealed no significant difference between these regressions (slopes and intercepts) (Figure 2).

DISCUSSION

This study evaluated the cardiorespiratory and perceptual responses of patients with coronary artery disease to graded recumbent and upright cycle ergometry. At a standard submaximal power output (100 watts), upright exercise was performed at a greater physiologic cost than was recumbent cycle ergometry. Although responses to maximal exercise were not significantly different, the recumbent position yielded a longer exercise time and a higher power output (177 vs 154 watts). Previous studies reported no difference[2] or even a decrease[1] in maximal exercise duration or work load achieved with supine versus upright exercise. Our results are in contrast to the data of Proctor et al[6] and Walsh-Riddle and Blumenthal,[7] but in agreement with the findings of Smith et al.[8]

Relative $\dot{V}O_2$ and HR at 100 watts were 15 and 10% lower, respectively, in the recumbent than in the upright position. Attenuated cardiorespiratory responses to submaximal recumbent ergometry may be attributed to reduced external work (i.e., weight of the legs did not have to be raised against gravity), increased internal muscular efficiency, or both.[9-11] These factors likely contributed to the increased peak power output and exercise time when subjects pedaled in the recumbent po-

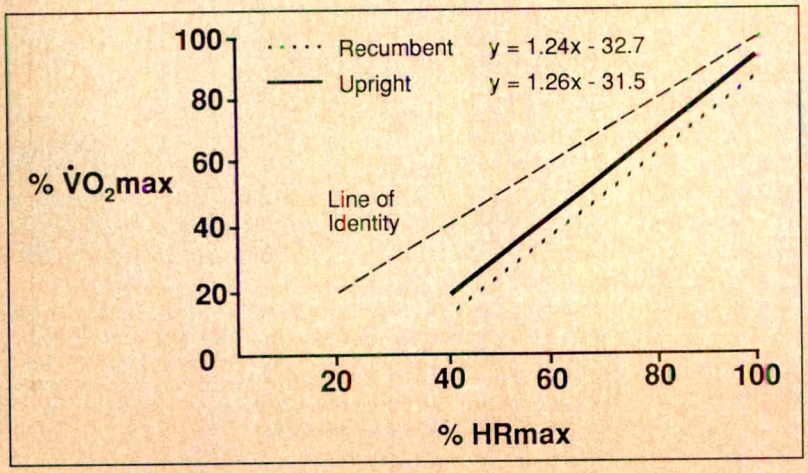


FIGURE 2. Recumbent and upright regression lines show similar relation between submaximal oxygen uptake (% $\dot{V}O_2$max) and heart rate (% HRmax). In the formula, y = % $\dot{V}O_2$max, and x = % HRmax.

sition. In contrast, total body energy output and caloric expenditure were unaffected by body position, because peak somatic $\dot{V}O_2$ was comparable during upright and recumbent exercise (22.6 vs 22.7 ml/kg/min).

Oxygen pulse, calculated by dividing $\dot{V}O_2$ by HR, has been shown to be a good relative measure of the stroke volume times the arterial-mixed venous oxygen difference of the blood.[12,13] The greater $\dot{V}O_2$ at the standard submaximal work rate (100 watts) during upright exercise was primarily attributed to a greater HR, because oxygen pulse was not significantly different between upright and recumbent ergometry (Table III). Alterations in venous return on left ventricular contractility and stroke volume may have also contributed to the differences in cardiorespiratory responses.

Perceptual responses to recumbent and upright exercise were assessed by the Feeling (enjoyment)[4] and conventional Borg[3] scales. Although enjoyment ratings were not significantly different, 8 of 14 patients preferred the recumbent to the upright ergometer, 3 preferred the upright ergometer and the remaining 3 had no preference. Perceived exertion ratings seemed to parallel somatic and myocardial aerobic requirements. At 100 watts, patients perceived recumbent cycling to be significantly easier than upright exercise (10.7 vs 11.7; $p < 0.001$). Accordingly, submaximal $\dot{V}O_2$, HR and blood pressure responses were also decreased. At peak exercise, however, cardiorespiratory and perceptual responses were not significantly different.

The present data have implications for exercise prescription. Although the exercise prescription for recumbent or upright training should ideally be derived from the results of an ergometer-specific test, this may not always be practical. In determining exercise guidelines it is important to establish 2 variables: the appropriate HR during training; and the work rate that will elicit a sufficient metabolic load for training.[14]

In the present study, maximal HR and $\dot{V}O_2$ responses to recumbent and upright ergometry were not significantly different. Because recumbent and upright exercise regressions of % $\dot{V}O_2$max on % HRmax were nearly identical (Figure 2), a given percentage of HRmax during recumbent cycling results in a percentage of recumbent $\dot{V}O_2$max comparable to that during upright exercise. These findings have major practical significance to the clinician who may prescribe upright exercise using the peak HR and $\dot{V}O_2$ values obtained during recumbent radionuclide ventriculography (e.g., stress multiple gated image acquisition analysis scans),[15] and thus obviating the need for additional exercise studies.

Based on data from other studies of men (Table IV) (Oja P, unpublished doctoral dissertation, Pennsylvania State University, 1973),[16–22] the value for the slope of the regression equations (% $\dot{V}O_2$max on % HRmax) varied from 1.2 to 1.5; the intercept varied between −24 and −52. With 1 exception,[18] these studies showed remarkably similar regressions of % $\dot{V}O_2$max on % HRmax. Such agreement indicates that the relative oxygen cost (% $\dot{V}O_2$max) of steady-state or nonsteady-state work can be predicted from HR alone.

TABLE IV Estimated Percentage of Maximal Oxygen Consumption (% $\dot{V}O_2$max) at Selected Percentages of Relative Heart Rate (% HRmax) from the Regression Equations for % $\dot{V}O_2$max on % HRmax for Studies Involving Men

Investigators	Exercise Mode	Slope	Intercept	% HRmax: 70	% HRmax: 85
				% $\dot{V}O_2$max	
Londeree & Ames[16]	TM	1.37	−41	55	76
Hellerstein et al[17]	CE	1.41	−42	57	78
Hellerstein et al[17]*	CE	1.32	−35	57	77
Saltin et al[18]	TM	1.20	−34	50	68
Taylor et al[19]	TM, CE	1.44	−43	58	79
Fardy et al[20]	CE	1.30	−36	55	74
	AE	1.20	−29	55	73
Skinner & Jankowski[21]	TM	1.50	−52	53	76
Oja†	TM	1.28	−29	61	80
Katch et al[22]	CE	1.39	−45	53	73
Present study*	CE	1.26	−32	57	76
	RE	1.24	−33	54	73

*Cardiac patients.
†Unpublished doctoral dissertation, Pennsylvania State University, 1973.
AE = arm ergometer; CE = cycle ergometer; RE = recumbent ergometer; TM = treadmill.

Furthermore, these studies show remarkably similar regressions of % $\dot{V}O_2$max on % HRmax, despite differences in subject age, presence or absence of coronary artery disease, fitness classification ($\dot{V}O_2$max vs age), training status, muscle groups exercised or testing modality.

In establishing the work rate for exercise training it is important to emphasize that although maximal physiologic responses to recumbent and upright ergometry are similar, cardiorespiratory and perceptual responses to recumbent exercise are decreased for any given power output. Consequently, a power output considered appropriate for upright exercise training will likely need to be increased for recumbent training.

An advantage of the recumbent cycle ergometer appears to be its use in patients with limited cardiorespiratory reserves. At a standard submaximal power output, aerobic requirements are significantly lower during recumbent than during upright exercise. The recumbent cycle also allows patients to achieve the same maximal HR and energy expenditure as upright ergometry, but over a wider power output range. Therefore, it is applicable to subjects with higher functional capacities as well.

Study limitations: These findings cannot be extrapolated to all cardiac patients. The low-risk patients in this study had undergone ≥4 months of physical training that may well have influenced their cardiorespiratory responses to exercise. Moreover, our data are probably not applicable to patients with myocardial ischemia or congestive cardiac failure. Previous reports indicate that the supine posture is an important potentiator of exercise-induced myocardial ischemia.[1] In such studies, the degree of ST-segment depression was significantly greater during exercise in the supine posture for a given HR. This concern, however, would likely be attenuated, because the recumbent (leaning) position

used in this study is between supine and upright exercise.

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Prognostic Significance of Exercise Thallium-201 Testing in Patients Aged ≥70 Years with Known or Suspected Coronary Artery Disease

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The prognostic value of exercise thallium-201 myocardial perfusion imaging has not been studied in an elderly (aged ≥70 years) population. Retrospective analysis of 120 consecutive elderly patients undergoing Bruce protocol exercise stress with quantitative planar thallium-201 scintigraphy, followed clinically for a mean of 36 ± 12 months after testing, revealed a 10% cardiac event rate (6 cardiac deaths from arrhythmia or congestive heart failure, and 5 fatal and 1 nonfatal myocardial infarction). There were no exercise stress-related complications. Survival without cardiac events was associated with greater exercise duration (5.6 ± 2.4 vs 3.1 ± 2.4 minutes; p <0.0007) and peak exercise heart rate (131 ± 18 vs 120 ± 19 beats/min; p <0.05). Univariate variables associated with higher cardiac event rates included: (1) peak exercise ≤ stage I (18 vs 6%; p = 0.04); (2) maximal ST-segment depression ≥2 mm (27 vs 6%; p = 0.003); and (3) presence of a fixed or reversible thallium-201 perfusion defect (18 vs 2%; p = 0.004). Multivariate stepwise logistic regression analysis identified the combination of peak exercise ≤ stage I and any thallium-201 perfusion defect as the most powerful predictor of subsequent cardiac events (relative risk = 5.3 at 1 year). Thus, exercise thallium-201 scintigraphy in elderly patients is safe and provides important prognostic information. Based on the peak Bruce protocol exercise stage achieved and presence or absence of a thallium-201 perfusion defect, most elderly patients (64%) can be stratified into very low- and high-risk groups with annual cardiac events rates of <1 and >15%, respectively.

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Stress thallium-201 scintigraphy is a widely used noninvasive procedure for the detection and prognostic assessment of patients with suspected or proven coronary artery disease.[1–7] Elderly patients represent a growing subset of such patients, with a high prevalence of multivessel and asymptomatic coronary artery disease.[5,8–13] The mortality and morbidity associated with coronary angioplasty[14–18] and coronary artery surgery[18–22] is significantly greater in elderly patients. Thus, the need exists for a noninvasive test that can distinguish between low-risk patients for whom cardiac catheterization and coronary revascularization can be safely postponed and high-risk patients for whom coronary revascularization may be indicated despite increased operative risk. Elderly patients frequently have noncardiac limitations to exercise (e.g., anxiety or musculoskeletal disorders) that may prohibit the performance of an adequate exercise test. Although previous reports examined the clinical role of exercise testing in elderly patients,[23–25] the prognostic value of exercise testing with thallium-201 scintigraphy has never been separately analyzed in a subset of patients aged ≥70 years who are capable of performing exercise stress. The present study retrospectively evaluates the prognostic use of exercise thallium-201 testing in patients aged ≥70 years.

METHODS

Patient selection and follow-up: The records of 2,623 consecutive subjects who had undergone exercise testing at our institution from January 1986 to March 1987 were reviewed, and 120 patients aged ≥70 years who had exercise thallium-201 scintigraphy according to the Bruce protocol were identified. All patients were referred for exercise testing for evaluation of known or suspected coronary artery disease.

Three years after testing, patients, or their families or referring physicians were contacted by telephone by an experienced cardiac research nurse. A medical questionnaire was completed to determine presence or absence of myocardial infarction, hospitalization, coronary bypass surgery or coronary angioplasty since the index stress test. Cardiac events were prospectively defined as cardiac death and fatal or nonfatal myocardial infarction. Medical records were used to confirm all cardiac events. State records were obtained to confirm absence of death in 16 patients who could not be contacted by telephone.

Three patients who did not perform exercise according to the Bruce protocol were excluded. Two patients

TABLE I Patient Characteristics

Variable	Event-Free (%)	Event (%)	p Value	All Pts. (%)
Number	108 (90)	12 (10)		120
Age (years)	74 ± 4	72 ± 2	0.25	74 ± 4
Men	66 (63)	9 (75)	0.41	75 (63)
Known CAD	57 (53)	6 (50)	0.86	63 (53)
Suspected CAD	51 (47)	6 (50)	0.86	57 (47)
Previous MI	28 (26)	3 (25)	0.93	31 (26)
History of CHF	9 (8)	1 (8)	0.99	10 (8)
Previous CABG	17 (16)	2 (17)	0.94	19 (16)
Previous PTCA	23 (17)	2 (22)	0.8	25 (21)
β blockers	22 (20)	2 (17)	0.76	24 (20)
Calcium antagonists	55 (51)	7 (58)	0.82	62 (52)
Nitrates	49 (45)	7 (58)	0.39	56 (47)
Digitalis	16 (15)	5 (42)	0.02	21 (18)
Abnormal ECG	80 (74)	10 (83)	0.48	90 (75)
ECG LVH	5 (5)	5 (42)	0.0001	10 (8)

CABG = coronary artery bypass grafting; CAD = coronary artery disease; CHF = congestive heart failure; ECG = electrocardiogram; LVH = left ventricular hypertrophy; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

TABLE II Exercise Test Results

	Event-Free (n = 108)	Events (n = 12)	p Value	Total (n = 120)
Rest SBP	131 ± 21	135 ± 14	0.54	131 ± 20
Peak SBP	166 ± 31	159 ± 31	0.43	166 ± 31
Rest DBP	82 ± 11	85 ± 15	0.25	82 ± 12
Peak DBP	85 ± 15	91 ± 19	0.22	86 ± 16
Rest HR	73 ± 14	68 ± 10	0.21	73 ± 14
Peak HR	131 ± 18	120 ± 19	0.05	130 ± 18
Rest HR*	75 ± 15	69 ± 10	0.18	74 ± 14
Peak HR*	134 ± 16	121 ± 21	0.02	133 ± 17
Exercise duration (min)	5.6 ± 2.4	3.1 ± 2.4	0.0007	5.3 ± 2.5 (1–12)
% PMHR	89 ± 12	81 ± 13	0.03	88 ± 12
% PMHR*	92 ± 11	82 ± 14	0.01	91 ± 11

*Excluding patients receiving β blockers.
DBP = diastolic blood pressure; HR = heart rate; PMHR = predicted maximal heart rate; SBP = systolic blood pressure.

had technically inadequate thallium-201 images and were excluded from this analysis.

Exercise testing: A symptom-limited exercise test was performed using the Bruce protocol. Patients were fasting, and cigarette smoking was curtailed ≥2 hours before testing. Cuff blood pressure measurements were obtained at rest in the standing position, every 3 minutes during exercise, at peak exercise and every minute for ≥5 minutes during recovery. A 3-lead electrocardiogram was monitored continuously, and 12-lead electrocardiograms were recorded every 3 minutes during exercise and every 1 minute for ≥5 minutes during recovery. An ischemic ST-segment response was defined as ≥1 mm horizontal or downsloping ST-segment depression 80 ms beyond the J point in 3 consecutive leads compared with baseline. In the presence of repolarization abnormalities on the electrocardiogram at rest or for patients taking digitalis, an abnormal response was considered present if there was ≥2 mm of excess horizontal or downsloping ST-segment depression 80 ms beyond the J point compared with at baseline. There were no adverse cardiac events during exercise testing.

Thallium-201 myocardial perfusion imaging: At peak exercise, 2 mCi of thallous chloride were injected intravenously while the patient continued exercising for 30 to 60 additional seconds. Planar thallium-201 imaging was initiated within 5 minutes of the injection using a small field of view gamma camera (Elscint, New Jersey) equipped with a low-energy, high-resolution, parallel whole collimator. Sequential images were obtained in the 45° left anterior oblique, anterior and left lateral views. These images were obtained at the 80 KeV photo peak with 20% window and stored on a 256 × 256 byte computer matrix. Approximately 500,000 counts were obtained over 10 minutes for each image. Redistribution images were obtained in identical views at approximately 4 hours after termination of thallium-201 infusion. Images were viewed by 2 expert observers unaware of the study protocol who graded 5 myocardial segments per view as being normal or as a fixed or reversible perfusion defect.[26] Quantitative analysis of regional thallium-201 clearance was determined by subtraction of delay from poststress circumferential count profiles, with the derived washout curve compared with a validated normal file.[27]

Data analysis: Continuous variables are expressed as mean ± 1 standard deviation. Comparison of continuous variables in patients with and without cardiac events was performed using the unpaired or paired Student's *t* test. Discrete variables were compared with contingency tables and chi-square analysis. Analysis of variables predictive of cardiac events was performed using univariate and multivariate stepwise regression analyses using a commercially available software program. No interdependent variables were entered in the multiple regression model. Life table analyses were performed using actuarial methods. Differences were considered significant at $p < 0.05$.

RESULTS

Patient characteristics (Table I): One hundred twenty patients were evaluated with a mean follow-up duration of 36 ± 12 months. Mean age for patients at the time of exercise thallium-201 study was 74 ± 4 years (range 70 to 88), and 63% were men. Fifty-three percent of the patients had definite coronary artery disease on the basis of coronary angiography (>50% diameter stenosis) and 26% on the basis of a documented myocardial infarction; 47% had suspected coronary artery disease on the basis of clinical evaluation. Patients with subsequent cardiac events had significantly greater prevalence of digitalis use and electrocardiographic left ventricular hypertrophy than did event-free surviving patients.

There were 12 cardiac events (10%) at 36 ± 12 months of follow up (6 myocardial infarctions [1 nonfatal] and 6 cardiac deaths from arrhythmia or congestive heart failure). Fifteen patients underwent coronary revascularization subsequent to exercise testing (9 had coronary artery surgery and 6 had coronary angioplasty). Eight early (<3 months) revascularization procedures were excluded from analysis of end points because of the possibility that revascularization was directly influenced by the exercise thallium-201 findings.

Exercise thallium-201 testing results (Table II): Mean exercise duration was 5.3 ± 2.5 minutes (range 1

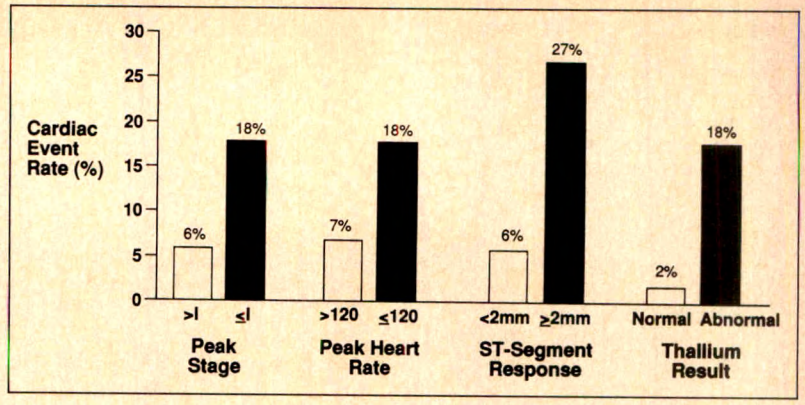


FIGURE 1. Cardiac event rates at 36 ± 12 months were higher in patients with peak exercise stage ≤stage I (p = 0.04), peak heart rate ≤120 beats/min (p = not significant), ≥2 mm horizontal or downsloping ST-segment depression (p = 0.003), or abnormal (fixed or reversible) thallium-201 image (p = 0.004).

to 12) (Table II). Exercise duration and mean peak heart rates were significantly greater in event-free surviving patients than in those with subsequent cardiac events (Figure 1). The peak heart rate difference was more pronounced when patients not receiving β-blocker medications were analyzed separately (Table II). The percentage of predicted maximal heart rate achieved was significantly greater in event-free surviving patients than in those with subsequent cardiac events (89 ± 12 vs 81 ± 13%; p = 0.03). This difference was similarly more pronounced in patients not receiving β-blocker therapy.

Thirty-eight patients (32%) did not achieve a peak exercise stage greater than Bruce stage I (Table III). The cardiac event rate for these patients was significantly greater than that observed for the 82 (68%) who achieved a final exercise stage greater than stage I (18 vs 6%; p = 0.04; Figure 1).

Twenty-two patients (18%) had ≥2 mm ST-segment depression at peak exercise (Table III). The cardiac event rate for these patients was significantly higher than that observed for 98 (82%) with <2 mm ST-segment depression (27 vs 6%; p = 0.003; Figure 1). ST-segment depression <2 mm did not significantly predict the occurrence of cardiac death or myocardial infarction. However, ST-segment depression <2 mm did predict the need for late (>3 months) subsequent revascularization. The 6 patients who underwent late revascularization had greater ST-segment depression (1.8 ± 1.1 vs 0.7 ± 0.9 mm; p = 0.004).

TABLE III Cardiac Event Rates at 36 Months by Exercise Thallium-201 Test Results

	No. (%)	Cardiac Event Rate (%)
Peak stage		
I	38 (32)	18*
II	62 (52)	6
III to IV	20 (16)	5
ST response		
<2 mm	98 (82)	6†
≥2 mm	22 (18)	27
Thallium-201 results		
Normal	62 (53)	2‡
Fixed	27 (23)	11
Reversible	15 (13)	20
Combined	14 (12)	29

*p = 0.04 (comparing ≤ to > stage I); †p = 0.003; ‡p = 0.006.

Most patients (53%) had normal thallium-201 images. Only 2% of these patients had subsequent cardiac events during follow-up. This rate was significantly lower than that observed for patients with fixed, reversible or combined (both fixed and reversible) thallium-201 defects (11, 20 and 29%, respectively; p = 0.0006; Table III and Figures 1 and 2).

Patients were divided into low-, intermediate- and high-risk groups using 2 stratification schemes (Table IV). In the exercise risk category, patients were stratified into low-, intermediate- and high-risk groups based on peak exercise stage (≤ or > Bruce stage I) and presence or absence of ≥2 mm ST-segment depression (Table V). Low-, intermediate- and high-risk groups had cardiac event rates of 4, 14 and 33%, respectively, over

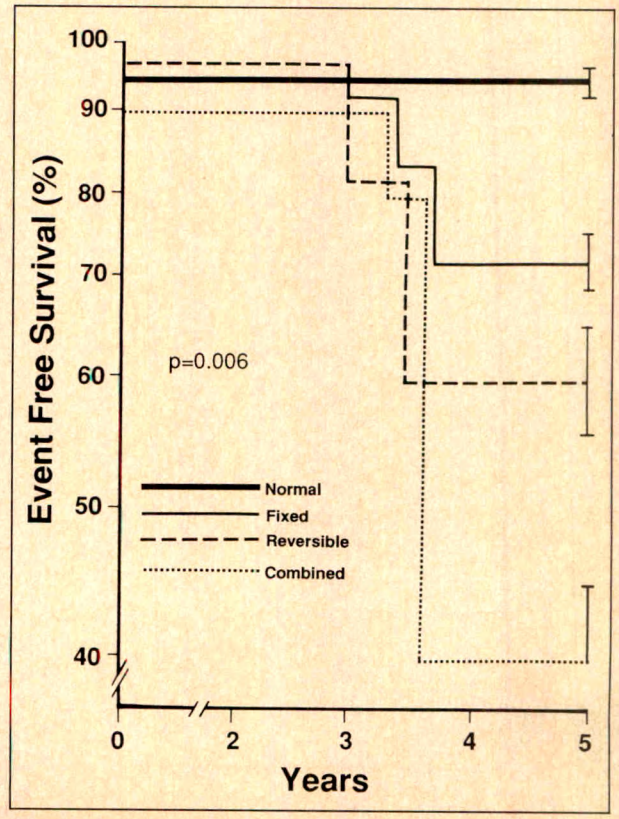


FIGURE 2. Five-year event-free survival curves for patients with normal thallium-201 images compared with those for patients with fixed, reversible and combined (fixed and reversible) thallium-201 perfusion defects.

TABLE IV Definitions of Risk Categories

Exercise risk category
Low—final exercise stage > Bruce stage I, and < 2 mm ST-segment depression
Intermediate—final exercise stage ≤ Bruce stage I, or ≥ 2 mm ST-segment depression (not both).
High—final exercise stage ≤ Bruce stage I, and ≥ 2 mm ST-segment depression
Thallium-201 risk category
Low—final exercise stage > Bruce stage I, and no thallium-201 defect
Intermediate—final exercise stage ≤ Bruce stage I, or a thallium-201 defect (not both)
High—final exercise stage < Bruce stage I, and a thallium-201 defect

TABLE V Cardiac Event Rates at 36-Month Follow-Up Based on Exercise and Thallium-201 Risk Categories (see Table IV for definitions)

	No. (%)	Cardiac Event Rate (%)
Exercise risk category*		
Low	71 (59)	4
Intermediate	37 (31)	14
High	12 (10)	33
Thallium-201 risk category†		
Low	60 (51)	2
Intermediate	43 (36)	7
High	15 (13)	47

*p = 0.006; †p = 0.0001.

36 months (p = 0.006; Figure 3). In the thallium-201 risk category, patients were divided into low-, intermediate- and high-risk groups based on peak exercise stage (≤ or >Bruce stage I) and presence or absence of any thallium-201 defect (Table V). Low-, intermediate- and high-risk groups had cardiac event rates of 2, 7 and 47%, respectively (p = 0.0001; Figure 4).

Multivariate stepwise logistic regression analysis was performed on variables with previously reported prognostic significance[1-3] and on significantly prognostic variables identified by univariate regression analysis. High thallium-201 risk category was strongly predictive of subsequent cardiac events (p = 0.0001; relative risk = 5.3). Variables that did not contribute further to the predictive power of the multiple stepwise regression model included: high exercise risk category; age; history of myocardial infarction; history of congestive heart failure or coronary revascularization; digitalis or β-blocker use; electrocardiographic evidence of left ventricular hypertrophy; peak exercise heart rate; and ST-segment response to exercise.

DISCUSSION

The mean age of patients referred for coronary angioplasty[13] and bypass surgery[28] has increased in the past decade. Proper risk stratification and selection of elderly patients for coronary revascularization are critical owing to the increased risk of these procedures in the elderly.[13,14,18,19] Previous studies document the poor outcome of elderly patients who cannot perform exercise testing.[23] In the present study, elderly patients who could perform Bruce protocol exercise stress tests with thallium-201 scintigraphy were stratified on the basis of

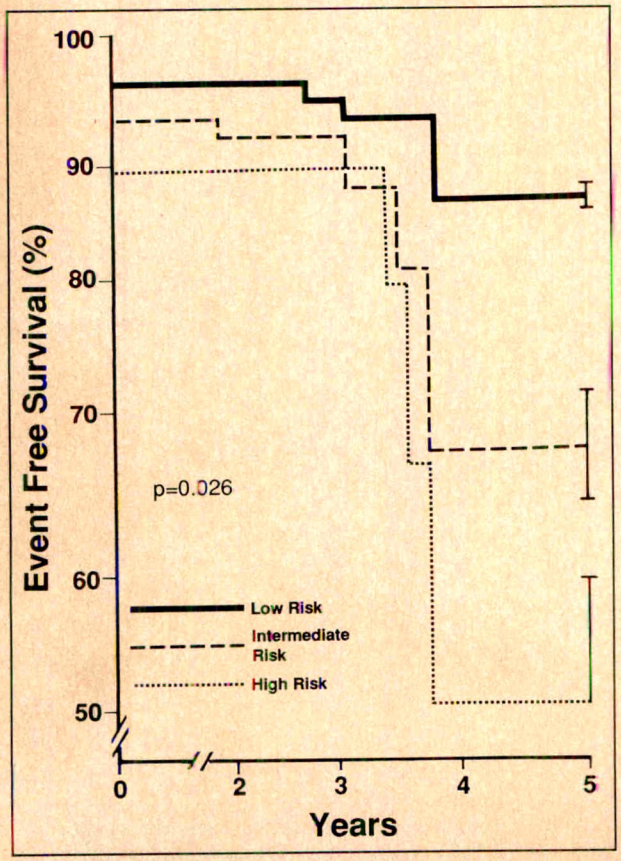


FIGURE 3. Five-year event-free survival curves based on thallium-201 risk category (see Table IV for definitions).

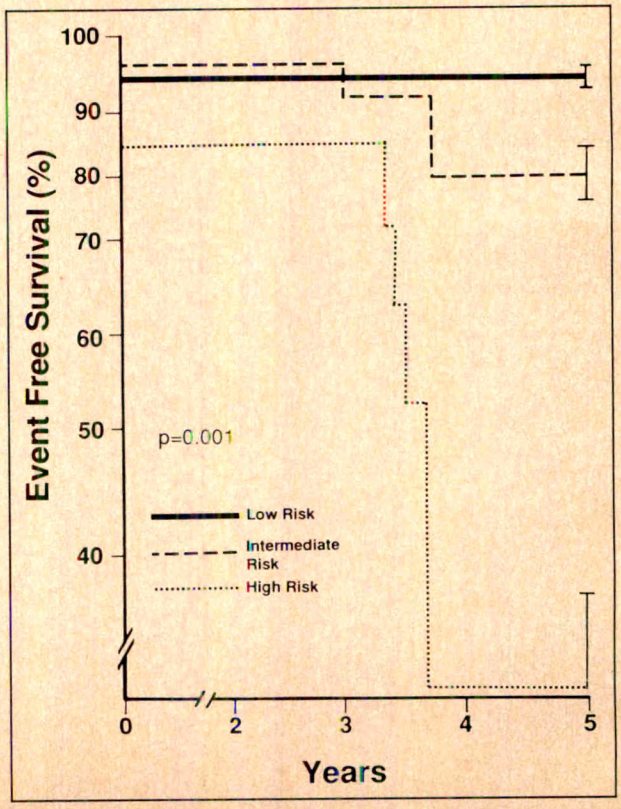


FIGURE 4. Five-year event-free survival curves based on exercise risk category (see Table IV for definitions).

final exercise stage and presence or absence of a thallium-201 defect into low-, intermediate- and high-risk subgroups for subsequent cardiac events. Importantly, 75 of 120 (64%) patients could be stratified into very low- and high-risk groups with annual cardiac event rates of <1 and >15%, respectively. Based on clinical evaluation and exercise test results, most elderly patients can be appropriately referred for medical therapy (low-risk group) or cardiac catheterization and subsequent coronary revascularization when appropriate (high-risk group). Based on peak exercise stage (≤ or > Bruce stage I) and presence or absence of an ischemic ST-segment response to exercise, 93 of 120 (69%) patients were stratified into low- and high-risk groups with annual cardiac event rates of <2 and >10%, respectively. Previous studies confirmed that decreased exercise tolerance is an important adverse prognostic finding.[29,30] Risk stratification may therefore be possible without nuclear techniques, potentially allowing important cost savings. However, thallium-201 scintigraphy allowed for a greater ability to discriminate between patients destined to have cardiac events and those not.

The prevalence of exercise electrocardiographic abnormalities was high (75%) in this elderly population. ST-segment abnormalities at rest (i.e., digitalis effect 18%, left ventricular hypertrophy 8%) may detract from the accuracy of exercise electrocardiographic findings and may partially explain the better prognostic information provided by thallium-201 data. ST-segment depression <2 mm was associated with a significantly increased rate of late (>3 months) coronary revascularization without an increased rate of cardiac death or myocardial infarction. Presumably, coronary revascularization prevented cardiac death in some patients with <2 mm ST-segment depression. However, contrary to Podrid et al,[31] profound (≥2 mm) ST-segment depression was associated with a significantly increased cardiac event rate. This difference is likely attributable to the advanced age of the present population (74 vs 57 years) and is possibly due to a higher prevalence of multivessel coronary artery disease in the elderly.[8–12]

Patients aged ≥70 years who are referred for coronary angiography have a 23% incidence of left main or 3-vessel coronary artery disease.[8] Despite the high prevalence of severe coronary artery disease and the generally low levels of exercise achieved in the present study, a normal thallium-201 image was associated with an excellent prognosis. More than half of the patients (53%) had normal stress thallium-201 images. In these patients, the annual cardiac event rate was <1%, confirming the observation of Iskandrian et al[4] who found a <1% annual cardiac event rate in a younger population (mean age 65 years) with normal thallium-201 images.

The current study was retrospective and may therefore be limited by preselection bias favoring a group of elderly patients who were able to perform exercise testing and were likely perceived by their referring physicians as potential candidates for revascularization despite their advanced age.

Bruce exercise protocol thallium-201 myocardial perfusion imaging is prognostically useful in elderly patients and allows for risk stratification of most patients (64%) to either a low- or high-risk subgroup. One quarter of the elderly population have either reversible (13%) or fixed plus reversible (12%) thallium-201 perfusion defects that are associated with annual cardiac event rates of 7 and 10%, respectively. Prospective decision analysis is needed to examine the annualized cost saved per year of life using exercise thallium-201 imaging in approximately one third (36%) of elderly patients who are at intermediate risk for cardiac events (2.3% annually).

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Feasibility of High-Dose Dipyridamole-Magnetic Resonance Imaging for Detection of Coronary Artery Disease and Comparison with Coronary Angiography

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To assess the feasibility, safety and usefulness of gradient-echo magnetic resonance imaging (MRI) combined with pharmacologic stress testing for the detection of coronary artery disease, 23 patients without previous myocardial infarction but with significant stenosis (>70% diameter stenosis) of ≥1 major coronary artery were selected for dipyridamole-MRI stress testing. Each patient underwent MRI at rest, and high-dose dipyridamole-MRI (0.75 mg/kg over 10 minutes) of corresponding basal and midventricular short-axis tomograms. Additionally, these patients performed symptom-limited exercise stress tests. All short-axis tomograms were evaluated on a standardized segmental basis by grading each segment as normal, hypokinetic, akinetic or dyskinetic. Dipyridamole-MRI was considered pathologic if segmental wall motion deteriorated by ≥1 grade after dipyridamole. For comparison with coronary angiography, segmental wall motion gradings were related to the respective coronary artery territories in the short-axis plane.

Pathologic dipyridamole-MRI was obtained in 18 of 23 (78%) patients. For 1- and 2-vessel diseases, sensitivity was 69 and 90%, respectively. Exercise stress tests were pathologic in 14 of 23 (66%) patients. For 1- and 2-vessel diseases, sensitivity of exercise stress test was 58% (7 of 12 patients) and 77% (7 of 9), respectively. Sensitivity/specificity of dipyridamole-MRI for the localization of the stenosed coronary artery was 78/100% for left anterior descending, 73/100% for left circumflex, and 88/87% for right coronary artery stenoses.

It is concluded that dipyridamole-MRI is a feasible nonexercise-dependent test for detection and localization of functionally significant coronary artery disease.

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Experimental and clinical studies of both transmural and subendocardial ischemia demonstrated impairment of regional left ventricular function as the earliest and most evident sign of acute myocardial ischemia.[1-3] Thus a high-resolution and noninvasive method for wall motion analysis would have important clinical value for the detection and localization of functional, significant coronary artery disease (CAD). Currently available noninvasive imaging techniques have limitations in assessing regional wall motion. Optimal echocardiographic image acquisition depends on the skill of the operator and the presence of an adequate acoustic window. With radionuclide ventriculography, limited spatial resolution and overlap of both ventricles may render interpretation difficult.[4]

Gradient-echo magnetic resonance imaging (MRI) is a noninvasive method that permits acquisition of images with high-spatial and improved temporal resolution in any tomographic plane, making MRI a promising technique for the evaluation of ventricular function.[5,6] However, exercise stress testing using MRI has been limited by motion artefacts and space restriction.[7] Therefore, alternative means of provoking acute myocardial ischemia are needed that can be used in conjunction with MRI. In the presence of significant CAD, dipyridamole can induce myocardial ischemia[8] and has proved to be a suitable substitute for dynamic exercise in thallium-201 perfusion imaging[9] and echocardiography.[10] Pennell et al[11,12] were the first investigators to report on dipyridamole-induced wall motion abnormalities and reduced systolic wall thickening by MRI observed in a heterogeneous group of patients with variable severity of CAD. In their study, dipyridamole-MRI-assessed wall motion abnormalities had a sensitivity for the detection of CAD similar to that with planar thallium-201 imaging.[12] The present study was designed to assess the feasibility, usefulness and safety of a high-dose dipyridamole-MRI stress test in a homogeneous group of patients with the diagnosis of severe CAD by coronary angiography. To relate MRI findings to the coronary angiogram, segmental wall motion abnormalities were analyzed in 2 short-axis tomograms and compared with a standardized pattern of regional myocardial perfusion.

METHODS

Patients: Twenty-three patients (22 men and 1 woman, mean age 60 ± 8 years, range 47 to 79) without significant wall motion abnormalities at rest, but

TABLE I Clinical, Angiographic, Dipyridamole-MRI and Exercise Stress Findings

Pt. No.	Age (yr) & Sex	Coronary Angiography (coronary artery % diameter stenosis)			Dipyridamole-MRI: Clinical Findings		Dipyridamole-MRI: MRI Wall Motion Gradings Related to Angiography			Bicycle Exercise Stress Test (clinical findings and ST-depression >2mm)		
		LAD	LC	Right	Angina	ΔHR	LAD (B/M)	LC (B/M)	Right (B/M)	Angina	ST Depression	WL
1	47 M	0	90	70	+	11	n/n	p/p	p/p	0	0	75
2	48 M	0	100	0	+	15	n/m	p/n	p/p	0	0	125
3	49 F	80	0	80	+	18	n/n	n/n	n/n	0	0	50
4	50 M	100	0	90	++	29	p/p	n/n	p/p	+	V2-V4	125
5	52 M	80	0	0	++	35	p/n	n/n	n/n	+	0	125
6	52 M	90	0	0	+	35	n/n	p/p	p/p	+	V4-V6	150
7	53 M	100	0	0	+++	52	p/p	n/n	n/n	+	V4	75
8	57 M	90	0	0	++	30	p/p	n/n	n/n	0	0	150
9	57 M	70	0	0	+	20	p/p	n/n	n/n	0	0	75
10	58 M	70	0	100	++	33	p/p	n/n	p/p	0	V4-V6	125
11	59 M	0	70	80	+	35	n/n	p/p	p/p	+	0	100
12	61 M	0	90	100	++	15	n/n	p/p	p/p	+	V2-V6	75
13	62 M	0	90	0	0	21	n/n	n/n	n/n	0	V6	125
14	62 M	0	70	0	+	23	n/n	p/p	n/n	0	0	125
15	63 M	100	90	0	++	20	p/p	p/p	n/n	+	V4-V6	75
16	65 M	90	80	0	+	30	p/p	p/p	n/n	+	V4/V6	75
17	66 M	0	80	0	++	14	n/n	p/p	p/p	0	V4-V6	125
18	66 M	0	90	0	0	12	n/n	n/n	n/n	0	V6	100
19	67 M	90	0	80	0	10	p/p	n/n	p/p	0	LBBB	100
20	68 M	80	0	0	++	29	p/p	n/n	p/p	0	V5,V6	75
21	68 M	0	90	100	++	25	n/n	n/n	p/p	+	V4-V6	100
22	70 M	80	0	0	0	15	n/n	n/n	n/n	0	0	125
23	79 M	90	0	0	0	12	n/p	n/n	n/n	0	LBBB	75

B/M = basal/midventricular short-axis tomogram; ΔHR = difference in heart rate before and after dipyridamole infusion; LAD = left anterior descending coronary artery territory; LBBB = left bundle branch block; LC = left circumflex coronary artery territory; MRI = magnetic resonance imaging; n = normal dipyridamole-MRI in the territory of a patent vessel; n = normal dipyridamole-MRI in the territory of a severely stenosed vessel; p = pathologic dipyridamole-MRI in the territory of a severely stenosed vessel; p = pathologic dipyridamole-MRI in the territory of a patent vessel; Right = right coronary artery territory; WL = maximal work load achieved in watts; 0 = no angina; + = mild angina; ++ = moderate angina; +++ = severe angina.

with severe coronary artery stenoses by coronary angiography were included in this study (Table I). All patients who underwent MRI at rest and after dipyridamole infusion had discontinued calcium antagonist and β-blocker medication for 24 hours. All patients were asked to stop coffee or tea consumption 12 hours before dipyridamole-MRI. The period between the performance of coronary angiography, exercise stress testing and dipyridamole-MRI ranged from 1 to 10 days. Before inclusion in this study, informed consent was obtained from each patient as part of the study protocol.

Selective coronary angiography: Multiple views of each coronary artery were obtained. Coronary artery narrowing was assessed as % diameter stenosis using electronic calipers. Regional left ventricular wall motion was evaluated visually and graded as normokinetic, hypokinetic, akinetic or dyskinetic. Only patients with normal wall motion and ≥1 high-grade stenosis (>70% diameter stenosis) of a major coronary vessel or main branch were selected for dipyridamole-MRI.

Exercise stress testing: All patients performed a multistage upright bicycle ergometer test beginning with a work load of 25 W and subsequent increments of 25 W every 2 minutes. A 12-lead electrocardiogram (ECG) and blood pressure were recorded every minute. Criteria for interrupting the test were severe angina, ST-segment depression >2 mm, maximal age-related heart rate or muscular exhaustion. Exercise stress testing was considered pathologic if typical angina pectoris developed or the ECG showed downsloping or horizontal ST-segment depression >2 mm, from baseline at 80 ms from the J point.

Rest and dipyridamole-magnetic resonance imaging: Oblique images (i.e., true short-axis images of the heart) were obtained by using a commercially available 1.5-Tesla superconducting magnet (Philips Gyroscan S15). The gradient-echo technique employed low flip angles of 30° and gradient refocused echoes with an echo time of 12 ms. Repetition time was 28 ms. The acquisition matrix was 128 × 256 interpolated to 256 × 256 for display. Pixel size was 1.25 × 1.25 mm. Multislice, sagittal, coronal and transaxial electrocardiographically gated localizing spin-echo sequences were obtained to define the cardiac axes. Then 2 short-axis tomograms perpendicular to the long axis of the left ventricle with a slice thickness of 8 mm encompassing the basal and midventricular levels of the left ventricle were selected for further analysis. Measurements were repeated 4 times to improve signal-to-noise ratio. Total imaging time ranged from 30 to 40 minutes and was determined by the subject's heart rate. After obtaining MRI at rest, a standardized high-dose dipyridamole test was performed without removing the patient from the magnet.[13] Each patient was injected with dipyridamole (Persantine; 0.75 mg/kg) over a period of 10 minutes. In the absence of angina, an additional bolus of dipyridamole (0.25 mg/kg) was injected in the patients. Five minutes after termination of dipyridamole infusion, di-

pyridamole-MRI encompassing the same short-axis tomograms as the MRI at rest was performed; then, 0.24 g of aminophylline was injected into the patients before termination of the study.

Image analysis: For each tomogram, the image obtained at the R wave of the ECG was considered to represent end-diastole. Using electronic tracing of the endocardial border, and software provided by the manufacturer, the center of mass was determined in each tomogram. An adhesive screen mask was used to divide each tomogram in 8 segments by equally spaced radii of 45°. The individual location of the screen mask was defined by superimposing the center of the screen mask to the endocardial center of mass, and rotational alignment of the bold radiant (Figure 1) to the junction between the interventricular septum and the right ventricular free wall. With the screen mask in this position, cine-display of MRI images was performed for qualitative evaluation of myocardial function at rest and after dipyridamole infusion. Segmental wall motion was graded as hypokinetic if wall motion and systolic wall thickening were reduced but not absent. A segment graded as akinetic was considered to have no systolic wall thickening and severe hypokinesis or akinesis. A segment graded as dyskinetic had systolic outward movement of the endocardial border, and no systolic wall thickening or thinning. All tomograms were analyzed by 2 observers who were unaware of the coronary angiographic findings. When there was a disagreement as to the grading of segments, a third observer reviewed the study, and the subsequent majority judgment was binding. A normal wall motion response to dipyridamole-MRI was defined as the development of hyperkinetic wall motion, or preservation of the contraction pattern at rest after dipyridamole infusion. A pathologic dipyridamole-MRI needed development of transient wall motion abnormalities in a segment that was graded normal at rest. To predict which coronary artery would be stenosed, the location of segments with normal and pathologic wall motion as assessed by dipyridamole-MRI was compared with the presumed territory of the main coronary arteries (Figure 1). A stenosed coronary artery was considered to be present if at least 1 segment related to the respective coronary artery territory was pathologic by dipyridamole-MRI. If no segment was abnormal, the corresponding coronary artery was thought to be not significantly stenosed.

Statistical analysis: Values were expressed as mean ± standard deviation. Student's paired *t* test was used to assess hemodynamic differences before and after dipyridamole-MRI. Overall sensitivity of dipyridamole-MRI for the detection of CAD was defined as the percentage of all patients with CAD and pathologic dipyridamole-MRI according to the equation: true pathologic/(true pathologic + false normal) × 100. Sensitivity for the correct identification of stenosed coronary arteries was defined as the percentage of correct dipyridamole-MRI findings/(correct dipyridamole-MRI + false normal dipyridamole-MRI) × 100. Specificity for the detection of normal coronary arteries was defined as the percentage of true normal dipyridamole-MRI/(true normal dipyridamole-MRI + false normal dipyridamole-MRI) × 100. The null hypothesis was rejected at the 95% confidence level, with a p value <0.05 considered to be significant.

RESULTS

Coronary angiography (Table I): In all, 33 coronary artery stenoses with >70% diameter narrowing were identified by 2 angiographers. Thirteen patients had 1-vessel disease, and 10 had 2-vessel disease. All patients had normal left ventricular wall motion at ventriculography.

Exercise stress test (Table I): All patients performed exercise stress tests. In 14 patients, typical angina or significant ST-segment depression, or both, developed during exercise stress testing. Two patients had complete left bundle branch block and did not develop angina. Among the other 7 patients with normal exercise stress tests, 4 did not reach the maximal predicted heart rate, and exercise was stopped because of muscular exhaustion. Excluding the 2 patients with left bundle branch block, overall sensitivity of exercise stress testing based on the development of angina or ST-segment depression was 66% (14 of 21). One- and 2-vessel disease sensitivities were 58 (7 of 12 patients) and 78% (7 of 9, respectively). The specificity of exercise stress testing could not be assessed, because all patients had abnormal angiograms.

Hemodynamic and symptomatic data during dipyridamole-magnetic resonance imaging (Table I): There was a significant (p <0.001) increase in heart rate of 23 ± 10 beats/min (range 11 to 52) after dipyridamole infusion. Blood pressure was not significantly different at rest and after dipyridamole infusion. Chest pain developed in 17 of 23 (74%) patients during dipyridamole infusion. Severe angina was reported in 9 of 23 (39%) patients, which was more accentuated than during exercise stress testing. After routine administration of 0.24 g of aminophylline at the end of dipyridamole-MRI, termination of angina occurred in 16 of 17 (94%) patients with angina. One patient with a subtotal left anterior

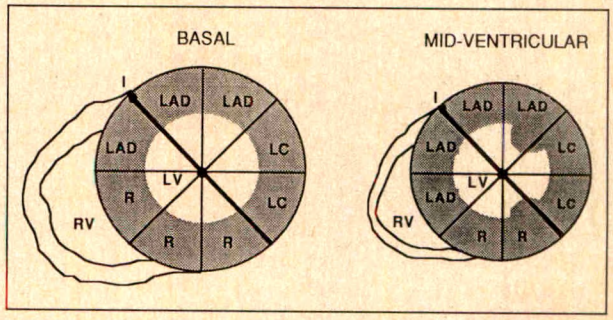


FIGURE 1. Segmental division of basal *(left)* and midventricular *(right)* short-axis tomograms. Bold radiant was aligned to junction between interventricular septum (I) and right ventricular free wall (RV), followed by equally spaced radii of 45° emanating from endocardial center of mass of left ventricle (LV). The 8 segments encompassing entire left ventricular circumference were related to respective coronary vascular territory with respect to location of short-axis tomogram (basal, midventricular). LAD = left anterior descending; LC = left circumflex; R = right coronary artery.

descending coronary artery stenosis and good collateralization could not be relieved with aminophylline alone, and additional nitrate administration was needed. Minor side effects (headache, nausea and flushing) were frequent but well-tolerated by all patients.

Dipyridamole-magnetic resonance imaging (Table I): MRI at rest and dipyridamole-MRI studies were adequate for qualitative wall motion analysis in all patients (Figure 2). In this selected group of patients with severe CAD, 18 of 23 had a pathologic dipyridamole-MRI (i.e., an overall sensitivity of 78%). For patients with 1-vessel disease, the sensitivity for CAD was 69%. For patients with 2-vessel disease, the sensitivity was 90%.

Comparison with coronary angiography: Comparison of the presumed coronary artery territories (Figure 1) with the location of segments graded as normal/pathologic by dipyridamole-MRI yielded high sensitivities/specificities for the identification of patent/stenosed coronary arteries. The correct identification of the site of stenosis was possible in 11 of 14 myocardial regions (sensitivity 78%) supplied by a stenosed left anterior descending coronary artery. Two of the 3 patients without wall motion abnormalities did not develop angina during dipyridamole-MRI. No patient with a patent left anterior descending coronary artery had a pathologic dipyridamole-MRI in the respective territory (specificity 100%). Transient wall motion abnormalities occured in 8 of 11 coronary artery territories (sensitivity 73%) supplied by a stenosed left circumflex coronary artery. Two of 3 patients without wall motion abnormalities had 1-vessel disease and no angina during dipyridamole-MRI. The other patient had 2-vessel disease with stenosis of a dominant right coronary artery accounting for dipyridamole-induced wall motion abnormalities confined to the right coronary artery territory. In the right coronary artery territory, 7 of 8 stenosed vessels were detected by dipyridamole-MRI (sensitivity 88%). In contrast to a 100% specificity of dipyridamole-MRI achieved in the left anterior descending and circumflex coronary artery territories, wall motion abnormalities were observed in right coronary artery-related segments despite a patent right coronary artery reducing specificity of dipyridamole-MRI in this particular region to 87%.

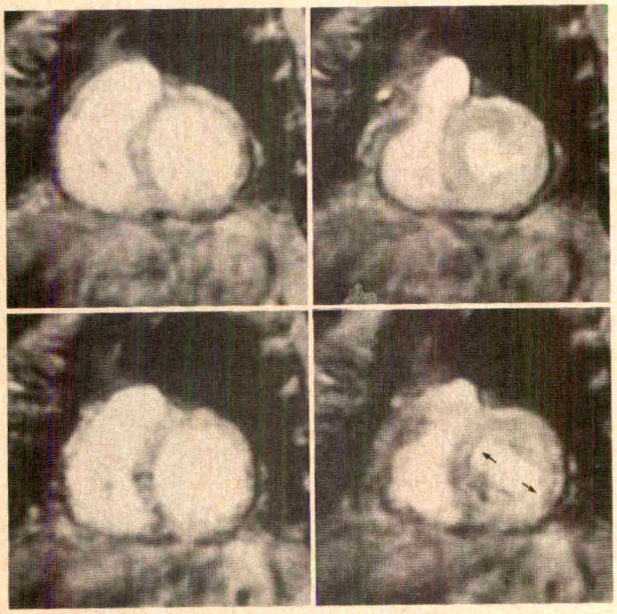


FIGURE 2. Magnetic resonance imaging (MRI) at rest and dipyridamole-MRI of patient with severe (>70%) stenoses of left anterior descending and circumflex coronary arteries. End-diastolic *(left)* and end-systolic *(right)* images from cine-loop of same midventricular short-axis tomogram obtained before *(top row)* and after *(bottom row)* dipyridamole infusion are shown. Note end-systolic lack of wall thickening in the septal and posterolateral regions *(arrows)* after dipyridamole *(bottom right).*

DISCUSSION

Safety of dipyridamole-magnetic resonance imaging: Our data indicate that dipyridamole-MRI can be safely performed in patients with significant CAD. Angina could be relieved in all but 1 patient who needed nitrates additionally. This is in agreement with studies showing the safety of dipyridamole echocardiography in patients with angina.[14,15]

Image quality: Adequate images were obtained in all patients before and after dipyridamole infusion. In some cases, increased breathing frequency due to severe angina led to a reduction in the excellent image quality of MRI at rest (Figure 2). However, even in these cases image quality was sufficient to perform segmental wall motion analysis.

Overall diagnostic accuracy of dipyridamole-magnetic resonance imaging: An overall sensitivity of 78% for the detection of CAD by pharmacologic induction of wall motion abnormalities is in agreement with dipyridamole echocardiography tests and is somewhat better than the sensitivities reported for dipyridamole radionuclide ventriculography tests. However, reported sensitivity for the detection of CAD by dipyridamole-induced wall motion abnormalities varies from 52 to 89% for dipyridamole echocardiography tests[16] and from 13 to 67% for dipyridamole radionuclide ventriculography.[17,18] The high sensitivity reported for dipyridamole-MRI can be explained by several factors: (1) imaging technique: As shown by Pflugfelder et al[6] MRI facilitates wall motion analysis by cinematic display of the dynamic changes during the heart cycle.[19] The high temporal and spatial resolution of MRI short-axis tomograms in conjunction with standardized segmental evaluation may have improved the detection of less severe and extensive wall motion abnormalities. (2) Patient selection: Patients with ≥70% stenoses of 1 coronary artery may have contributed to the high sensitivity of dipyridamole-MRI, because detectable wall motion abnormalities are more likely to occur in those with more severe or multivessel CAD.[16] This is also reflected by differing sensitivities for 1- (69%) and 2-vessel (90%) diseases in the present study. Therefore, it is possible that the good results obtained in this study cannot be reproduced in a cohort of patients with less severe

CAD. (3) Dosage of dipyridamole: The high dosage of dipyridamole that has been reported to increase diagnostic sensitivity of dipyridamole tests[13,15] may have contributed to the high sensitivity of dipyridamole-MRI. In this study, dipyridamole-induced angina was present in 17 of 23 patients yielding a sensitivity of 74% that is slightly less than that of dipyridamole-MRI for CAD. Because only patients with severe CAD were studied, the specificity of dipyridamole-induced angina versus dipyridamole-MRI–detected wall motion abnormalities could not be assessed.

In a recently published study Pennell et al[12] compared dipyridamole-MRI–induced wall motion abnormalities with thallium-201 perfusion imaging in a heterogeneous group of 40 patients with CAD with and without previous myocardial infarction and subsequent wall motion abnormalities at rest. The sensitivity of dipyridamole-MRI–induced wall motion abnormalities for CAD was 62%. The coincidence of reversible thallium defects and wall motion abnormalities was reported to be 67%. The better sensitivity for CAD found in the present study may be ascribed to the selection of patients with severe CAD and no previous myocardial infarction, facilitating the detection of dipyridamole-induced wall motion abnormalities. The higher dipyridamole loading dose may also have contributed to the better results in this study.

Identification of stenosed coronary arteries by dipyridamole-magnetic resonance imaging: Dipyridamole infusion can provoke regional myocardial ischemia in a vascular territory supplied by a severely stenosed coronary artery.[20,21] However, the precise physiology of dipyridamole-induced myocardial ischemia is not fully understood. A variety of flow and steal mechanisms leads to a reduction in subendocardial blood flow and subsequently to regional wall motion abnormalities.[22] In this study, the localization of segments with a pathologic dipyridamole-MRI yielded a good correspondence to the presumed vascular territories of stenosed coronary arteries defined with respect to the location of the short-axis tomograms; in particular, the sensitivity of dipyridamole-MRI was similar for left anterior descending and circumflex coronary artery stenoses (78 and 73%, respectively), with a specificity of 100%. For the detection of right coronary artery stenosis, the sensitivity was 88%. Two patients with severe left circumflex coronary artery stenoses were erroneously thought to have right coronary artery stenoses due to wall motion abnormalities in the diaphragmatic wall, reducing specificity for detection of right coronary artery stenosis to 87%. These false gradings can be explained by a dominant left coronary artery system in both patients supplying parts of the diaphragmatic myocardium. Similar problems were also reported in studies of dipyridamole echocardiography,[14,23] with good prediction of left anterior descending coronary artery stenoses, but problematic differentiation between left circumflex and right coronary artery stenoses.

Five patients with CAD could not be identified by dipyridamole-MRI. These patients were characterized by absent or only mild angina during dipyridamole-MRI. Four of these patients had 1-vessel disease, and none had a totally occluded coronary vessel. The heart rate increase during dipyridamole-MRI was not significantly different from that in patients with wall motion abnormalities. Interestingly, none of these 5 patients developed angina during exercise stress testing.

Study limitations: Several limitations of the present study merit comment. First, our data were obtained from a selected group of patients with severe CAD. Therefore, further studies are needed to assess whether similar feasibility, safety and diagnostic accuracy can be documented in patients with less severe stenoses. Second, the severity of stenoses was not measured using quantitative computerized angiography, which may have resulted in erroneous classification of stenosis severity. However, electronic caliper measurements as used in this study were shown to provide similar accuracy.[24] Third, a quantitative approach[25] with assessment of mean segmental diastolic and systolic wall thicknesses, and calculation of systolic wall thickening for MRI at rest and dipyridamole-MRI instead of segmental wall motion analysis may have been more accurate. However, this quantitative approach is time consuming and depends on excellent image quality that could not be achieved in all patients during dipyridamole-MRI. The final limitation is related to the long imaging time of dipyridamole-MRI. Despite the fact that after dipyridamole infusion, scanning time was shorter due to the increase in heart rate, and our study protocol was confined to a basal and midventricular short-axis tomogram, scanning time was still long and uncomfortable for patients with dipyridamole-induced angina. The routine use of fast imaging techniques[26] may solve this problem and allow the acquisition of tomograms in different projections to obtain a more representative examination of the heart with a minimum of discomfort for the patient.

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Intracoronary Urokinase as an Adjunct to Percutaneous Transluminal Coronary Angioplasty in Patients with Complex Coronary Narrowings or Angioplasty-Induced Complications

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The effectiveness of intracoronary urokinase infusion as an adjunct to percutaneous transluminal coronary angioplasty (PTCA) was studied in 50 patients who underwent angioplasty for complex coronary narrowings or had thromboembolic complications during PTCA (29 [58%] men, 3 [6%] stable and 37 [74%] unstable angina, and 16 [32%] prior coronary bypass surgery). The primary indications for intracoronary urokinase infusion were intracoronary thrombus in 27 patients (54%), distal coronary embolization in 9 (18%), and abrupt reclosure in 14 (28%). Urokinase was infused in a mean (± standard deviation) dosage of 399,000 ± 194,000 IU (range 150,000 to 1,000,000) at an average rate of 5,000 to 20,000 IU/min. Angiographic success was achieved in 43 patients (86%). Complications included the need for urgent bypass surgery in 3 patients, Q-wave myocardial infarction in 2, and non-Q-wave myocardial infarction in 12 (8 of whom had peak creatine kinase less than twice the upper normal limit). The incidence of myocardial infarction was significantly higher in patients with vein grafts (69%) than in those with PTCA of native vessels (14%). Two patients died (1 massive gastrointestinal necrosis 24 hours after angioplasty, and 1 after urgent bypass surgery). Mean (± standard deviation) fibrinogen levels were 355 ± 73 mg/dl before urokinase infusion, and 361 ± 70, twelve hours afterward. Three patients had local bleeding, but no transfusions were needed. It is concluded that intracoronary urokinase is a safe and effective adjunct to PTCA in patients with associated thrombi and may improve the success rate in angioplasty complicated by thrombus formation.

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As the indications for percutaneous transluminal coronary angioplasty (PTCA) expand, the procedure is used in more complex, high-risk situations such as unstable angina and other acute ischemic syndromes. Intracoronary thrombolysis in unstable angina was first described in the early 1980s by Rentrop et al[1] and Vetrovec et al[2] using streptokinase. Subsequent studies were conducted using intravenous or intracoronary thrombolysis in patients with unstable ischemic syndromes and in conjunction with PTCA.[3-7]

In patients with unstable ischemic syndromes, complex coronary narrowings (including intravascular thrombi and ulcerated plaques) are recognized as forerunners of complications with angioplasty.[8-11] The fact that patients' outcomes are improved by prolonged heparin administration before, during and after angioplasty[12,13] demonstrates the importance of thrombus stabilization and suggests a role for thrombolytic therapy as an adjuvant to angioplasty. This study investigated the effectiveness of intracoronary urokinase infusion in the following 2 settings: (1) as an adjunct to angioplasty in patients with significant narrowing of complex morphology; and (2) as an intervention in those undergoing angioplasty complicated by acute thrombotic closure or distal embolization, or both.

METHODS

Patients: This study retrospectively reviews 50 consecutive patients who underwent intracoronary urokinase infusion in conjunction with PTCA at the Medical College of Virginia from April 1988 to December 1989. Patients were either at high risk for acute complications because of the presence of large intracoronary thrombus or had an acute occlusive complication with flow compromise during angioplasty. Patients were grouped according to the indications for which intracoronary urokinase was administered. One group of 27 patients (54%) received urokinase for angiographic evidence of intracoronary thrombus. Eight of these patients received urokinase before the angioplasty procedure owing to angiographic evidence of extensive thrombotic mass (Figure 1), and the remaining 19 received urokinase during the procedure (Figure 2). The second group consisted of 9 patients (18%) with distal thrombotic embolization during angioplasty (Figure 3). The third group consist-

ed of 14 patients (28%) who developed abrupt reclosure while in the catheterization laboratory after an apparently successful balloon dilatation, and it was believed by the operator that thrombus was the predominant factor responsible for acute closure. Patients with angiographic evidence of dissection as a major etiologic factor of acute closure were excluded from this study and treated with other modalities such as prolonged balloon inflations, directional atherectomy, laser balloon angioplasty or coronary bypass surgery.

Infusion technique: Before the procedure, patients were administered aspirin and a calcium antagonist; then, 10,000 IU of heparin were administered as a bolus. A repeat bolus of 3,000 to 5,000 IU of heparin was administered every hour during angioplasty (by standard technique). Urokinase was infused through the guiding catheter or distal port of the balloon catheter proximal to the thrombus. In cases of total occlusion, urokinase was administered before or after wire penetration of the occlusion site. Urokinase was diluted in normal saline solution (5,000 IU/ml) and infused manually at a rate of 5,000 to 20,000 IU/min. The total dose was determined by angiographic evidence of thrombolysis on sequential angiographic testing. Thrombolysis was defined as a significant decrease in thrombus mass or an improvement in anterograde flow, or both. Continuous heparinization was maintained for ≥24 hours after the procedure; mean length of heparinization was 3.5 days (range 1 to 11). Coagulation parameters including prothrombin time, activated partial thromboplastin time and plasma fibrinogen levels were measured before the procedure, and 12 hours afterward before sheath removal.

Definitions: Intracoronary thrombus was defined as an intraluminal filling defect adjacent to a stenosis seen in multiple views. Thrombotic occlusion was defined as a blunt occlusion with contrast staining. Ulcerated plaque was defined as extraluminal pouching with or without eccentric or "jagged" borders. A non-complex lesion was defined as a discrete lesion with smooth borders and no intraluminal filling defects. Lesion severity was visually assessed by 2 angiographers experienced in angioplasty. The degree of stenosis was assessed from the view that demonstrated the most severe narrowing.

Urokinase lysis was defined as complete resolution or obvious reduction in thrombus size. Absence of lysis was defined as either no change or increase in thrombus mass. Procedural angiographic success after PTCA was defined as ≤50% residual stenosis and restoration of

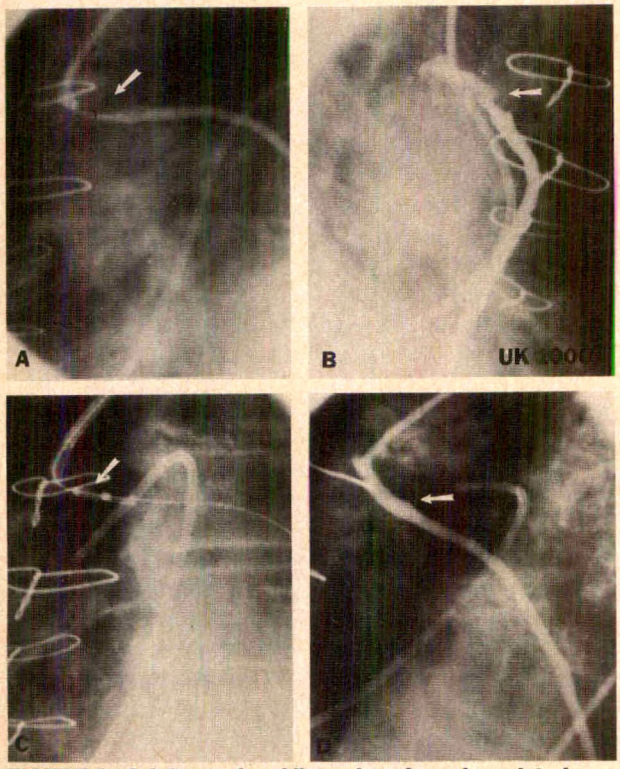


FIGURE 1. ***A,*** **left anterior oblique view shows large intraluminal filling defect in proximal segment of circumflex vein graft** ***(arrow).*** ***B,*** **marked reduction in thrombotic mass, and improvement in anterograde flow** ***(arrow)*** **after urokinase (UK) infusion (1,000,000 IU).** ***C,*** **directional atherectomy of proximal lesion performed subsequently.** ***D,*** **left anterior oblique view shows no significant residual narrowing in proximal portion of circumflex vein graft** ***(arrow).***

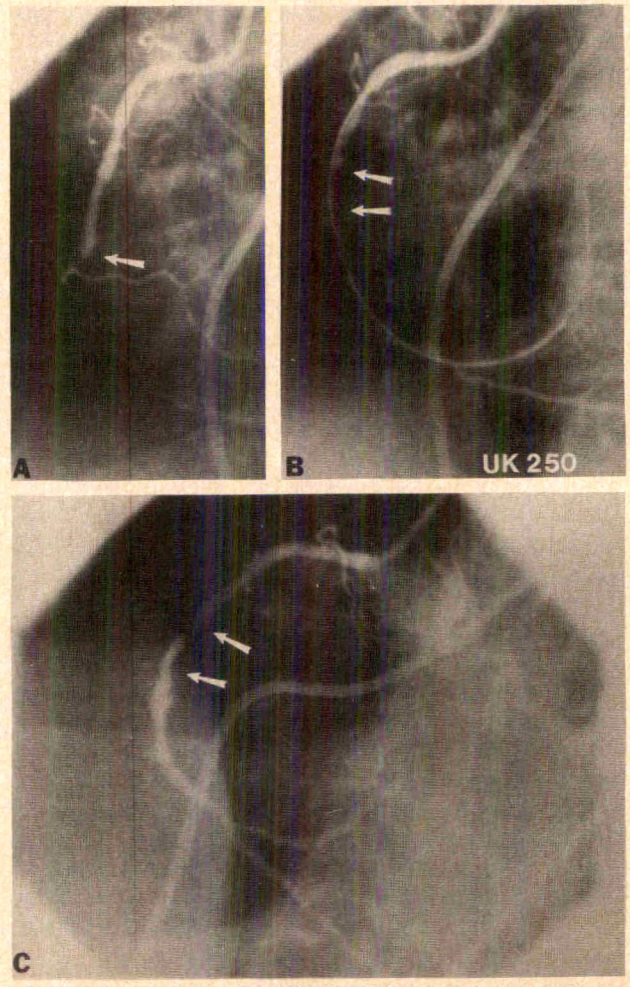


FIGURE 2. ***A,*** **left anterior oblique view shows thrombotic occlusion of right coronary artery** ***(arrow).*** ***B,*** **successful crossing of occlusion site with serial balloon inflations. Repeat angiography shows multiple intraluminal filling defects consistent with thrombus** ***(arrows).*** ***C,*** **marked improvement in luminal diameter with no residual intraluminal filling defect** ***(arrows)*** **after urokinase (UK) infusion (250,000 IU) and repeat balloon inflations.**

brisk anterograde flow. Clinical success was defined as angiographic success associated with clinical improvement of ≥1 functional class without a major in-hospital complication (excluding non-Q-wave myocardial infarction). Major complications were defined as myocardial infarction, need for emergency coronary bypass surgery, or death. Myocardial infarction was defined as creatine kinase elevation greater than the upper limit of normal, corrected for sex and race, with MB fraction >6%.

Statistics: Values are expressed as mean ± standard deviation. Chi-square testing was used for determination of discrete variables. A p value <0.05 was considered significant.

RESULTS

The 50 study patients included 29 men and 21 women, with a mean age of 59 ± 10 years. The clinical and angiographic characteristics of these patients are listed in Table I.

Treatment outcomes are listed in Table II. Urokinase lysis was observed in 40 patients (80%), and overall angiographic success was achieved in 43 (86%). Clinical success was achieved in 39 patients (78%). Mean urokinase dosage was 399,000 ± 194,000 IU (median 250,000, range 150,000 to 1,000,000). Mean plasma fibrinogen levels were 355 mg/dl at baseline and 361, twelve hours after urokinase administration (p = not significant).

Table II lists complications that occurred in the study patients. Urgent bypass surgery was required in 3 patients (6%) (2 had bypass surgery for persistent acute closure due to major intimal dissection, and the third for a thromboembolic complication of angioplasty). In all, 14 patients (28%) had myocardial infarction. However, 12 (24%) of these patients had a non Q-wave myocardial infarction (8 had peak creatine kinase less than twice the normal upper limit in our laboratory). Non-Q-wave myocardial infarction was due to persistent acute closure of a distal left anterior descending in 1 patient, to transient occlusion with successful restoration of anterograde flow in 5 and to distal embolization in the remaining 6. Q-wave myocardial infarction, occurring in 2 patients, was due to failed angioplasty and persistent total occlusion of a right coronary artery venous graft in 1 and to persistent distal embolization in a posterolateral branch after restoration of anterograde flow in an initially totally occluded native right coronary artery in the other. Two patients died during hospitalization (1 after urgent bypass surgery, and the other 24 hours after the balloon procedure from a massive mesenteric infarction).

Patients with intracoronary thrombus: Twenty-six of the 27 patients who received urokinase for intracoronary thrombus had thrombus evident before angioplasty, and the remaining patient had an ulcerated narrowing without thrombus. Urokinase dosage for these patients ranged from 250,000 to 1,000,000 IU (mean

TABLE I Clinical and Angiographic Characteristics of Patients Undergoing Urokinase Infusion (n = 50)

Clinical characteristics	
Men/women	29 (58%)/21 (42%)
Stable angina	3 (6%)
Unstable angina	37 (74%)
Rest angina	21 (42%)
Post–myocardial infarction angina (<15 days)	16 (32%)
Recent infarction (<21 days)	10 (20%)
Previous coronary artery bypass	16 (32%)*
Multivessel coronary artery disease	36 (72%)
Multivessel PTCA	6 (12%)
Angiographic characteristics	
Coronary artery dilated	
Left anterior descending	18 (36%)
Right	17 (34%)
Left circumflex	2 (4%)
Vein grafts	13 (26%)
Lesion present	
Thrombotic occlusion	24 (48%)
Intracoronary filling defects	15 (30%)
Ulcerated narrowings	12 (24%)
Noncomplex narrowings	8 (16%)

*Mean age of patients' grafts was 6.7 years (range 2 to 11).
PTCA = percutaneous transluminal coronary angioplasty.

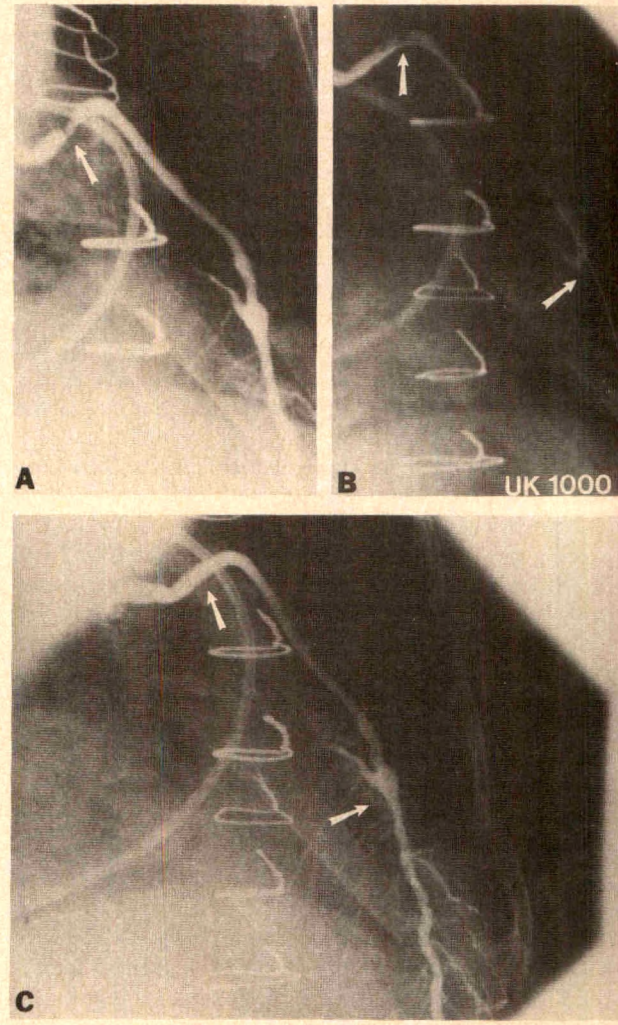


FIGURE 3. ***A,*** **right anterior oblique view showing very discrete proximal lesion of left anterior descending saphenous vein graft** ***(arrow).*** ***B,*** **significant intraluminal filling defect at initial site of dilatation seen on repeat angiography after initial angioplasty. Distal embolization occurred at distal insertion site to left anterior descending artery** ***(arrows).*** ***C,*** **restoration of anterograde flow with no residual intraluminal filling defects** ***(arrows)*** **after infusion of urokinase (UK) (1,000,000 IU) through guiding catheter, and repeat angioplasty.**

TABLE II Results of Urokinase in Patients with Intracoronary Thrombus, Distal Emboli and Acute Closure

	Patients with:				
	Intracoronary Thrombus (n = 27)				
	Urokinase Before Angio. (n = 8)*	Urokinase During Angio. (n = 19)	Distal Emboli (n =9)	Acute Closure (n = 14)	Overall (n = 50)
Results					
Urokinase lysis	7	16	8	9	40 (80%)
Angiographic success	7	17	9	10	43 (86%)
Clinical Success	6	15	9	9	39 (78%)
Complications					
Urgent CABG	0	1	0	2	3 (6%)
Death†	1	1	0	0	2 (4%)
Q-wave infarction‡	0	2	0	0	2 (4%)
Non-Q-wave infarction‡	1	6	2	3	12 (24%)
Entry site hematoma§					

*Four patients had saphenous vein graft involvement, and 4 had native vessel occlusion.
†One patient died after urgent coronary bypass, and the other died of massive mesenteric, infarction 24 hours after angioplasty.
‡Causes of myocardial infarction were acute closure (n = 2), transient occlusion (n = 5) and distal emboli (n = 7).
§Hematomas were small to moderate and needed no transfusions.
Angio. = angioplasty; CABG = coronary artery bypass graft.

429,100). In 8 patients, intracoronary urokinase was administered before balloon dilatation because of extensive thrombus, with the goal to decrease risk of acute closure and distal embolization. In 7 of these patients, thrombi either resolved completely (n = 1) or improved significantly (n = 6). Only 1 patient had no evidence of lysis, and balloon angioplasty failed with persistent subtotal occlusion of a native right coronary artery. Distal emboli were seen on the angiograms of 2 patients, but their enzymes were not elevated. In the 1 patient with non-Q-wave myocardial infarction, peak creatine kinase was 166 IU/liter (MB 9%).

Seventeen (89%) of the 19 patients in the intracoronary thrombus group who received urokinase in conjunction with repeat balloon inflation achieved angiographic success (treatment outcomes are listed in Table II). Procedural complications included 1 emergency bypass operation, because of acute thrombotic occlusion of the left anterior descending artery after balloon catheter exchange with subsequent cardiogenic shock; despite successful revascularization, the patient died within 4 hours. Although 8 of the 19 patients had either Q-wave or non-Q-wave myocardial infarction (n = 2 and 6, respectively), clinical success was achieved in 15.

Patients with distal embolization: The results of urokinase treatment in the 9 patients with distal embolization are listed in Table II. Urokinase dosage ranged from 250,000 to 1,000,000 IU (mean 472,000). Five patients had thrombus evident before balloon dilatation, with thrombotic occlusion present in 4. Four other patients initially had apparently "non-complex" significant narrowings. Urokinase infusion was begun in association with balloon inflation when distal embolization became evident, as indicated by an intraluminal filling defect distal to the dilatation site. Five of the 8 patients whose thrombi were lysed had complete resolution, and 3 had significant angiographic improvement of distal embolization with restoration of anterograde flow and reduced size of the filling defect. Two patients had small non-Q-wave myocardial infarction despite angiographic evidence of distal thrombolysis and no flow compromise. All 9 patients were clinically improved after angioplasty.

Acute closure: In the 14 patients with abrupt closure during angioplasty, the initial lesion was a thrombotic occlusion in 4 (including 1 vein graft), an ulcerated plaque in 2, a nonocclusive intracoronary thrombus in 4, and a non-complex lesion in 4. Urokinase dosage ranged from 150,000 to 500,000 IU (mean 289,000). In all 14 cases, repeat balloon dilatation with prolonged inflations did not achieve stable patency, and thrombus was thought to be the main cause of persistent closure. With the combined approach of intracoronary urokinase and repeat dilatation, angiographic success was obtained in 10 of these patients, and clinical success was achieved in 9. Two patients needed urgent bypass surgery for occlusion associated with major intimal dissection. One patient underwent elective bypass surgery for persistent symptoms despite successful angioplasty. Two others had persistent occlusion without complications; the initial lesion in both was a total occlusion. Three patients had a small non-Q-wave myocardial infarction with a peak creatine kinase less than twice the upper limit of normal; this was attributed to transient occlusion, with restoration of brisk anterograde flow in 2 patients. The third patient had persistent total occlusion of a distal left anterior descending segment.

Vein graft patients: When the results of combined urokinase infusion and angioplasty in vein grafts versus native vessels were compared, the outcomes were similar in both groups (Table III). However, the incidence of myocardial infarction (especially non-Q-wave) was significantly higher in the group with vein grafts (62 vs 11%; $p < 0.001$). The incidence of other complications including Q-wave infarction, need for urgent surgery, and death was similar in the 2 groups.

Total occlusion: Total occlusion was observed in 24 patients (48%) (involving vein grafts in 8, and native vessels in 16). Urokinase was administered for intracoronary thrombus in 7 vein grafts and 10 native vessels, for distal embolization in 4 native vessels, and for acute closure in 1 vein graft and 2 native vessels.

Angiographic success was achieved in all occluded vein grafts attempted (8) and in 15 of 16 totally occluded native vessels attempted. One patient had persistent occlusion attributed to major dissection. Presence of total occlusion before PTCA did not confer a higher complication rate (29% [7 of 24] compared with 42% [11 of 26] in patients with patent vessel before PTCA [p = not significant]).

TABLE III Treatment Outcome in Patients with Vein Grafts Versus Those with Native Vessels

	Vein Grafts (n = 13)	Native Vessels (n = 37)
Thrombolytic success	12 (92%)	29 (78%)
Angiographic success	12 (92%)	31 (84%)
Clinical success	11 (85%)	28 (76%)
Complications		
Myocardial infarction		
Q wave and non-Q wave	9 (69%)	5 (14%)*
Q wave only	1 (8%)	1 (3%)
Non-Q wave only	8 (62%)	4 (11%)*
Death	1 (8%)	1 (2%)
Urgent coronary bypass surgery	2 (15%)	4 (11%)

*p <0.001.

DISCUSSION

In all, urokinase lysis was successful in 80% of our patients (86% angiographically and 78% clinically successful). In 7 of our 8 patients with extensive intracoronary thrombus who had intracoronary urokinase infusion before angioplasty, thrombi resolved and subsequent balloon angioplasty was successful. Thus, most of our patients did not have the complications after angioplasty that would be expected.[14] Urokinase infusions were also effective in most patients (85%) who developed intraprocedural thrombi, and comparable success rates were found in patients who received urokinase for distal emboli. These results are comparable to those reported by Verna et al[15]; when these investigators managed thromboembolic complications of angioplasty with intracoronary urokinase infusion, their overall success rate increased from 10 to 65%, and the need for urgent surgical intervention decreased from 60 to 13%.

When abrupt reclosure occurred in our patients, the combined approach of urokinase and repeat balloon angioplasty was successful in 71% of the patients (10 of 14); only 2 needed urgent bypass surgery for major intimal dissection. In a series of 48 patients reported by Schieman et al,[16] only 1 (2%) needed emergency bypass surgery. These results suggest that urokinase infusion helps reestablish anterograde flow and decreases the need for urgent coronary bypass surgery in patients with PTCA complicated by thrombus formation.

In our series, myocardial infarction occurred in 28% of our patients, and urgent bypass surgery was needed in 6% (a higher percentage than was previously reported for routine angioplasty)[17]; however, most of the myocardial infarctions in our patients were of the non-Q-wave type (86%), and in two thirds of these, peak creatine kinase levels were less than twice the upper limit of normal. In many of these patients, the flow compromise leading to myocardial infarction was present before urokinase infusion as a complication of balloon angioplasty. When urokinase was used as an adjunct to repeat balloon dilatation, anterograde flow was restored, and the evolving infarction was interrupted.

Treatment outcomes were comparable in patients with PTCA of vein grafts and in those with PTCA of native vessels. However, patients with vein grafts had more complications, especially non-Q wave infarction. Whereas our recanalization rates were comparable to those previously reported for vein grafts,[18,19] the incidence of infarction in our patients was higher than that reported by Hartmann et al[18] and Marx et al[19]; it was comparable to that reported by De Feyter et al[20] and McKeever et al.[21] The high incidence of myocardial infarction could be explained either by mechanical fragmentation and dislodgement of thrombus or by atheroma or microemboli of thrombus during lysis.[20,21] Therefore, we believe that the choice of angioplasty for patients with diseased grafts should be made on a case-by-case basis and balanced with the risks of repeat bypass surgery.

Thus, our results suggest that intracoronary urokinase can be a useful adjunct to PTCA in patients with extensive intracoronary thrombus or in those in whom PTCA is complicated by thrombotic closure or distal emboli.

Study limitations: This is a descriptive study of urokinase in the setting of complicated PTCA, rather than a randomized controlled trial (i.e., urokinase infusion was the only treatment administered to patients with complicated PTCA, rather than urokinase versus no infusion). Randomization would have been inappropriate in the presence of the complications observed in these patients. Furthermore, dosage of urokinase was variable. However, rate and extent of clot lysis depend on age and magnitude of the thrombus, as well as on the thrombolytic agent used, and dosage and duration of infusion. Thus, dosage of urokinase was individualized according to the extent of thrombus present and of lysis observed. A large multicenter prospective study is currently in progress[22] to evaluate prognostic descriptors and results of intracoronary urokinase in association with complex PTCA.

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Peripheral Vascular Complications After Conventional and Complex Percutaneous Coronary Interventional Procedures

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To determine whether complex cardiovascular interventional procedures (including coronary stent implantation, directional atherectomy, aortic valvuloplasty, and the use of an intraaortic balloon pump or cardiopulmonary bypass support) are associated with an increased likelihood of vascular access site complications, 2,400 consecutive cardiac catheterization procedures were prospectively screened over a 12-month study period. Complications occurred in 35 patients after 39 procedures (1.6%) and included the need for vascular surgical repair (17 patients), blood transfusion (28 patients) and systemic antibiotic therapy (7 patients). The incidence of complications after 1,519 diagnostic studies was 0.6%, after 698 conventional coronary balloon angioplasties 2.6%, and after 183 complex interventions 6.0% ($p < 0.0001$); 43% of the complications occurred after procedures of >2 hours' duration and 14% occurred in patients in whom arterial sheaths remained in situ for >24 hours. Detailed demographic and procedural characteristics were compared between the 35 patients with vascular complications and 150 patients randomly drawn from a computerized database of the uncomplicated procedures performed during the screening period. By univariate analysis with correction for multiple comparisons, variables predicting the likelihood of vascular complications included: periprocedural use of heparin ($p < 0.001$) or fibrinolytic therapy ($p < 0.001$), arterial sheath size ≥8Fr ($p < 0.001$), patient age ≥65 years ($p = 0.01$), and the presence of peripheral vascular disease ($p = 0.03$).

The results of this study suggest that the overall incidence of access site complications is low but increases with the use of complex cardiovascular interventional procedures. Further refinements in the caliber of the new devices, vigilant monitoring of adjunctive anticoagulant therapy, and careful patient selection may reduce the morbidity and increase the safety of these procedures.

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Since the advent of diagnostic cardiac catheterization >25 years ago, the complexity of diagnostic and therapeutic coronary angiographic procedures has increased considerably. This has resulted, in part, from an expansion of the indications for percutaneous coronary intervention to include older and more hemodynamically unstable patients, and patients with more extensive coronary and peripheral vascular disease.[1–4] In addition, the introduction of a variety of new devices for the treatment of coronary arterial disease, including atherectomy catheters, metallic stents and circulatory support devices, has necessitated the use of both large caliber guiding catheters and arterial sheaths, and intensive periprocedural anticoagulant and fibrinolytic therapy.[5–7] The hazards associated with the use of these new devices include a potentially greater risk of arterial injury at the access site. Previous studies have reported the incidence of arterial complications after diagnostic cardiac catheterization[1–2,8–11] and percutaneous transluminal coronary angioplasty (PTCA),[3,12–15] but the incidence of peripheral vascular complications after more complex interventional procedures has not been systematically evaluated. The aims of this study, therefore, were (1) to characterize and to compare the risks of peripheral vascular injury after diagnostic cardiac catheterization, conventional PTCA, and complex coronary interventional procedures; and (2) to identify clinical and procedural factors that predict the likelihood of these complications.

METHODS

Patient selection and clinical assessment: All patients undergoing diagnostic or therapeutic cardiac catheterization at the University of Michigan Medical Center were prospectively evaluated over a 12-month study period. Each patient was interviewed and examined by a physician or physician's assistant immediately before the procedure. The clinical variables recorded included patient age, sex, height and weight, presenting symptoms, risk factors for arteriosclerotic disease, and the presence or absence of clinically detectable peripheral vascular disease. The procedural parameters recorded included the type of catheterization procedure performed, the size of the arterial and venous sheaths, the peri- or postprocedural use of antiplatelet, anticoagulant or fibrinolytic therapy, the duration of the procedure, the length of time from procedure completion until sheath removal, and the duration of bedrest after sheath removal. Patients undergoing outpatient diagnostic procedures were examined for evidence of access site complications immediately before discharge and were then interviewed by telephone 48 to 72 hours later. Pa-

tients remaining in the hospital were examined daily for the duration of the hospital stay. When vascular injury was suspected, duplex color flow Doppler imaging was performed as previously described,[16] and a vascular surgical opinion was obtained. All complications were prospectively recorded, and the subsequent course of each patient in this group was then followed to document the need for and timing of surgical repair, and the nature of the arterial injury as identified at the time of surgery. Details of the vascular surgical management of the peripheral vascular complications of cardiac catheterization procedures at our institution have been previously published.[17]

Procedural details: Ninety-nine percent of the cardiac catheterization procedures during the study period were performed from a percutaneous femoral arterial or venous approach; the remainder were performed from the brachial approach. Arterial punctures for diagnostic procedures were performed predominantly by junior cardiology fellows; those for interventional procedures were performed by senior cardiology fellows or by 1 of 6 attending physicians. Diagnostic procedures were performed through 6, 7 or 8Fr arterial sheaths. Heparin was not administered routinely during elective procedures; in stable patients, intravenous heparin infusions were discontinued ≥4 hours before arterial needle puncture. In patients undergoing emergency cardiac catheterization soon after the administration of thrombolytic therapy and heparin for acute myocardial infarction, the sheaths remained in situ after the completion of the procedure until the fibrinogen level had risen to ≥150 mg/dl and the activated partial thromboplastin time had returned to the normal range. All patients undergoing elective PTCA were pretreated with oral aspirin (325 mg/day) and received intraprocedural heparin (10,000 to 15,000 U intravenous bolus, then 5,000 U intravenously each hour). Therapy with heparin was not continued after uncomplicated procedures, and the sheaths (7 or 8Fr) were removed approximately 4 hours after the last heparin bolus. Patients with suboptimal angiographic results were treated overnight with an infusion of intravenous heparin (approximately 1,000 U/hour) and had their sheaths removed the following morning, 4 hours after discontinuation of heparin. Procedural details of the complex procedures have been previously described.[5–7] In brief, coronary stents were placed through 8, 9 or 10Fr guiding catheters and arterial sheaths, coronary atherectomy was performed through 11Fr guiding catheters, intraaortic balloon pumps were placed through 9.5 or 10.5Fr sheaths, aortic balloon valvuloplasty procedures were performed through 12 or 14Fr sheaths, and percutaneous cardiopulmonary support was instituted through 18 or 21Fr arterial and venous sheaths. The anticoagulation regimen for most complex interventions was similar to that described for conventional PTCA. Patients in whom coronary stents were implanted were pretreated with oral persantine and intravenous dextran (in addition to oral aspirin), and continued with infusion of heparin at therapeutic concentrations until oral anticoagulation with coumadin was established. Before sheath removal, the heparin infusion rate was reduced to 400 U/hour for a period of approximately 4 hours. The rate was then increased to the therapeutic rate 1 hour after sheath removal and the achievement of secure hemostasis. In patients in whom cardiopulmonary support was instituted, sufficient heparin was given to maintain the activated clotting time ≥300 seconds for the duration of the procedure. After completion of the procedure, sheaths were removed either by elective vascular surgical repair or by removal and prolonged compression after the clotting parameters had returned to normal.

Complications: Access site complications were defined as (1) local or retroperitoneal hemorrhage requiring the transfusion of ≥2 U of blood, (2) the need for surgical drainage or nonelective arterial repair of the access site, or (3) local or systemic infection requiring oral or intravenous antibiotic therapy. Patients undergoing elective surgical removal of cardiopulmonary support device sheaths were not included. The cardiac catheterization procedures performed were classified as diagnostic procedures (including right-sided cardiac catheterization, selective coronary angiography, left ventriculography and aortography), conventional coronary balloon angioplasty (including the adjunctive use of intracoronary or systemic fibrinolytic therapy) or complex interventional procedures. The latter classification included aortic balloon valvuloplasty, and the use of new percutaneous coronary revascularization devices (directional coronary atherectomy, endovascular stents or laser ablation catheters), or circulatory support devices (intraaortic balloon counterpulsation or percutaneous cardiopulmonary bypass). Predictive risk factors for peripheral vascular complications were identified by comparing the prevalence of selected clinical variables (patient age, presence of ≥3 risk factors for coronary arterial disease, and the presence of peripheral vascular disease) and procedural variables (arterial sheath size, and use of intraprocedural heparin or periprocedural fibrinolytic therapy) in the group of patients with access site complications and in a group of 150 patients randomly selected from the computerized database of event-free cardiac catheterization procedures.

Statistics: Differences in the incidence of complications between groups were compared using chi-square analysis. Univariate chi-square analysis with a Bonferroni correction for multiple comparisons was performed to identify individual clinical and procedural factors predicting the likelihood of arterial complications. A 2-tailed probability value <0.05 was considered statistically significant.

RESULTS

Access site complications: During the study period, 2,400 consecutive elective or emergency cardiac catheterization procedures were performed. These procedures included, 1,519 diagnostic procedures, 698 conventional coronary balloon angioplasties and 183 complex interventional procedures. The complex procedures included 69 coronary atherectomies, 25 coronary stent implantations, 34 aortic valvuloplasties, and the use of an intraaortic balloon pump in 45 patients and percutaneous

TABLE I Peripheral Vascular Complications: All Catheterization Procedures

Complications	Number (%)
Vascular	
Pseudoaneurysm	8 (21)
Laceration	6 (15)
Arterial occlusion	3 (8)
Arteriovenous fistula	3 (8)
Hematoma	1 (3)
Need for blood transfusion (≥2 U)	
With vascular surgery	14 (36)
Without vascular surgery	14 (36)
Sepsis	7 (18)
Death	2 (6)

TABLE II Demographic Variables and Peripheral Vascular Complications

Variable	Complication (%) (n = 39)	No Complications (%) (n = 150)
Age ≥65 years	20 (51)	39 (26)
Men/women	21/18 (54/46)	105/45 (70/30)
Systemic hypertension	22 (56)	56 (37)
Diabetes mellitus	12 (31)	56 (15)
Cigarette smoking	24 (62)	75 (50)
Hypercholesterolemia	22 (56)	55 (34)
Peripheral vascular disease	11 (28)	15 (10)
Obesity (body mass index ≥28 kg/m^2)	8 (21)	65 (43)

cardiopulmonary bypass support in 10 patients. Access site complications were identified in 36 patients (21 men, 15 women) after 39 procedures, each of which was performed using a percutaneous femoral arterial approach. The incidence of complications after diagnostic procedures was 0.6%, after conventional balloon angioplasty 2.6%, and after complex interventional procedures 6.6% ($p < 0.0001$) (Figure 1). Complications occurred in 4% of patients requiring intraaortic balloon counterpulsation, in 6% of patients undergoing atherectomy, 6% after aortic valvuloplasty, 8% after coronary stent implantation, and 20% after use of percutaneous cardiopulmonary support.

The complications encountered were predominantly associated with femoral arterial injury that occurred after 21 procedures (Table I). The most frequent injury was a femoral arterial pseudoaneurysm, which was identified by color flow Doppler imaging or at the time of surgery. Five of the 8 pseudoaneurysms were surgically repaired and 3 were treated conservatively. Each of the other vascular complications, including a femoral arterial laceration in 6 patients, arterial occlusion or thromboembolism in 3 patients, and femoral arteriovenous fistulas in 3 patients, required surgical treatment. Overall, surgical repair was required after 0.3% of diagnostic procedures, 0.7% of conventional angioplasty procedures and 3.8% of complex interventions ($p < 0.0001$) (Figure 1). Blood transfusion of ≥2 U of blood was required after 28 procedures (72%); 14 of these transfusions were administered to patients requiring vascular surgical repair of the access site and the remainder were

TABLE III Univariate Analysis of Risk Factors

Variable	Univariate Chi-Square	Corrected p Value	Odds Ratio	95% CI
Arterial sheath size ≥8Fr	23.3	<0.001	5.0	2.3–10.6
Thrombolytic therapy	29.0	<0.001	4.9	3.2–7.4
Periprocedural heparin	20.8	<0.001	4.2	2.1–8.6
Age ≥65 years	9.8	0.01	2.4	1.4–4.1
Peripheral vascular disease	8.2	0.03	2.4	1.4–4.3
≥3 coronary risk factors	2.3	0.06	2.3	1.3–4.0

CI = confidence interval.

administered to patients with local hemorrhage who were treated nonsurgically. Antibiotic therapy was administered to 7 patients (Table I), each of whom had infection limited to the local access site with no evidence of systemic infection by multiple blood cultures. One patient died from multisystem organ failure after diagnostic cardiac catheterization, and 1 patient died 24 hours after coronary balloon angioplasty from abrupt closure of the dilated right coronary artery. In this series, there were no postprocedural deaths after complex interventional procedures.

Demographic risk factors for vascular complications: When compared with the 150 randomly selected patients without complications, patients with access site complications tended to be older, had a greater prevalence of individual risk factors for atherosclerotic disease and a higher incidence of peripheral vascular disease, but had a lower incidence of obesity (defined as a body mass index ≥28 kg/m^2, where body mass index = weight/height^2) (Table II). By univariate analysis after correction for multiple comparisons, patient age ≥65 years and the presence of peripheral vascular disease remained statistically significant risk factors ($p = 0.01$ and $p = 0.03$, respectively) (Table III).

Procedural risk factors for vascular complications: The strongest procedural predictors of the likelihood of peripheral vascular complications were the use of large caliber introducing sheaths and the use of periprocedural anticoagulant and fibrinolytic therapy (Tables III

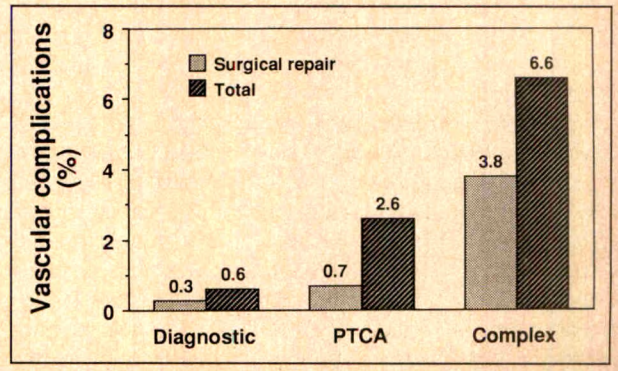


FIGURE 1. Comparison of the incidence of access site complications and need for surgical intervention in patients undergoing diagnostic cardiac catheterization, conventional percutaneous transluminal coronary angioplasty (PTCA), and complex cardiovascular interventional procedures. Differences between the groups were highly statistically significant ($p < 0.0001$).

TABLE IV Procedural Variables and Vascular Complications

Variable	Complication (%) (n = 39)	No Complications (%) (n = 150)
Procedure performed		
Diagnostic cardiac catheterization	6 (24)	100 (67)
Coronary angioplasty	18 (46)	38 (25)
Atherectomy	4 (10)	2 (1.3)
Stent	2 (5)	3 (2.0)
Valvuloplasty	2 (5)	3 (2.0)
Intraaortic balloon pump	2 (5)	2 (1.3)
Cardiopulmonary support device	2 (5)	1 (0.7)
Adjunctive therapy		
Preprocedural aspirin	36 (92)	110 (73)
Intraprocedural heparin therapy	32 (83)	53 (35)
Intraprocedural lytic therapy	11 (29)	2 (1.3)
Procedural details		
Arterial sheath size ≥ 8Fr	32 (82)	56 (37)
Procedure duration > 2 hours	17 (43)	5 (3)
Sheaths in situ > 24 hours	5 (14)	—

and IV). Arterial sheaths with a caliber ≥8Fr were used in 82% of patients who developed complications compared with 37% of those without complications ($p < 0.001$); arterial sheath sizes ≥9Fr were used in 29% of patients with arterial complications. Intraprocedural heparin was administered to 83% of patients with complications compared with 35% of event-free patients ($p < 0.001$), and fibrinolytic therapy was used in 29 and 1.4% of patients, respectively ($p < 0.001$). The preprocedural use of aspirin was also somewhat higher in the complicated group (92 vs 73%). In the group with arterial complications, 43% underwent cardiac catheterization lasting >2 hours, and in 14% the arterial sheaths remained in situ for >24 hours because of the periprocedural administration of fibrinolytic therapy or the need for uninterrupted postprocedural anticoagulant therapy.

DISCUSSION

The principal findings of this study are that the incidence of peripheral arterial complications after complex interventional procedures is significantly higher than after conventional diagnostic and therapeutic procedures. The incidence of complications was most closely associated with the use of large caliber introducing sheaths and the use of periprocedural anticoagulant or fibrinolytic therapy.

Vascular complications after diagnostic cardiac catheterization: Several large, multicenter registries[1,2,8,9] and single center studies[10,11] have documented the frequency of vascular complications after diagnostic cardiac catheterization. In studies that have excluded patients aged <1 year, the incidence of arterial complications has ranged from 0.2 to 1.9%, depending on the access site. In general, thrombotic ischemic arterial complications have been somewhat higher after procedures performed from the brachial approach than from the femoral route, but the latter approach has been associated with a higher incidence of hemorrhagic complications.[1,2,8–11] The overall incidence of 0.6% and the need for surgical repair in 0.3% in this study is comparable to that noted for femoral vascular access in the larger series.

Diagnostic procedures versus conventional percutaneous transluminal coronary angioplasty: The overall incidence of vascular complications after conventional PTCA in this study (2.6%), and the need for operative arterial repair (0.7%), also compare favorably with the frequencies quoted in previous reports. Two single center studies have compared the incidence of local vascular access site complications after diagnostic cardiac catheterization and conventional PTCA.[12,13] In these studies, coronary angioplasty was not associated with an increased incidence of complications but, in both studies, the frequency of vascular complications after diagnostic procedures was relatively high. In the study of Wyman et al,[12] surgical repair of the femoral artery was required after 1.6% of diagnostic procedures compared with 1.5% after coronary angioplasty, and Kaufman et al[13] noted an incidence of vascular complications of 0.9% after coronary angioplasty compared with 1.2% after diagnostic procedures. Three other studies have reported the incidence of peripheral vascular complications after PTCA.[3,14,15] In the 1977 to 1981 National Heart, Lung, and Blood Institute's PTCA registry of 1,500 patients,[3] local vascular complications occurred after 1.5% of the procedures, and in 2 large studies from Emory University, vascular complications occurred after 0.6% of 3,500 coronary angioplasties performed between 1980 and 1984,[14] and 1% of 4,988 PTCA procedures performed between 1985 and 1988.[15] In the latter study, peripheral vascular complications correlated strongly with patient age and the postprocedural use of heparin.

Complex coronary interventional procedures: Over the past 10 years, an increasing number of percutaneous coronary interventions have been performed in patients with unstable coronary syndromes, severe multivessel coronary artery disease, complex coronary lesion morphology, previous coronary artery bypass graft surgery and severely impaired left ventricular function.[4] In an effort to improve the safety of these high-risk procedures, a variety of new devices have been developed to reduce the likelihood of arterial dissection and abrupt closure, or to provide circulatory support in the event of profound myocardial ischemia and dysfunction. The use of these devices has necessitated the placement of large caliber catheters in peripheral arteries and veins, often in association with intensive anticoagulation or the administration of fibrinolytic therapy. Although previous reports have described the frequency of access site complications occurring after the use of some of these devices,[5,18] no study has previously compared the vascular morbidity of these new procedures with that of conventional coronary interventions.

One of the earliest devices used to increase the safety of conventional PTCA was the intraaortic balloon pump. Several studies have reported an increased incidence of vascular complications and sepsis after the use of these devices.[19–22] In these studies, the need for vas-

cular surgical repair ranged from 10.7 to 37%, and correlated with a history of diabetes mellitus,[19,21] the presence of peripheral vascular disease,[19] and with prolonged circulatory support (>20 days).[20] In the current study, the use of intraaortic balloon pumping for high-risk coronary interventions was associated with an incidence of access site complications of only 4.4%. The frequency of complications reported after the use of percutaneous cardiopulmonary support devices has also been high.[23,24] In 1 single center experience, vascular repair was required after 10% of procedures in which cardiopulmonary support was used, and 30% of the patients required blood transfusion.[23] Vascular morbidity was also high in a report from a multicenter cardiopulmonary support registry[24]; blood transfusion was required in 43% of 105 patients and significant arterial injury occurred in 26% of the study group. In the current study, 2 of 10 patients treated with percutaneous cardiopulmonary support required both nonelective vascular surgical repair and blood transfusion.

Relatively little has been published on the frequency of arterial complications after coronary atherectomy or stent implantation. In 1 study, vascular surgical repair was required in 2% of 67 patients after coronary atherectomy.[5] After Palmaz-Schatz stent implantation, 10 of 174 patients (5.7%) treated with the current intensive anticoagulant regimen required blood transfusion or vascular surgical repair.[18] In our own experience, although the incidence of access site complications was 8% in this study, the need for blood transfusion has been as high as 15% after elective stent implantation.[25,26] This high incidence of bleeding was attributed to excessive anticoagulation with heparin and has fallen considerably since the introduction of more vigorous monitoring of the patients' coagulation status. Aortic balloon valvuloplasty, another procedure requiring the use of large caliber introducing sheaths and balloon catheters, has been associated with major vascular complication rates ranging from 7 to 10%[12,27] and in 1 series[28] was associated with the need for leg amputation in 3 of 492 (0.6%) patients. A similar incidence of complications was noted in this study.

Clinical implications: In the current study, the strongest predictors of the need for vascular surgical repair, blood transfusion or systemic antibiotic therapy after percutaneous cardiovascular interventional procedures were the size of the arterial catheters, and the use of anticoagulant or fibrinolytic therapy. Patient age and the presence of peripheral vascular disease were also important variables, but patient gender, individual risk factors for coronary artery disease, obesity and the extent of coronary disease did not appear to be important factors. These findings suggest that the incidence of vascular complications might be reduced by further technical refinements such as a reduction in device caliber. In recent years, the caliber of directional coronary atherectomy catheters, intraaortic balloon pumps and the arterial and venous catheters of the percutaneous cardiopulmonary support device have all been effectively reduced. Furthermore, a reduction in the profile of both fixed-wire and over-the-wire balloon angioplasty systems has permitted an increasing number of coronary angioplasties to be performed through 6 and 7Fr guiding catheters.[29] Efforts to reduce the thrombogenicity of metallic stents are also clearly warranted so that the need for intensive antiplatelet and antithrombotic therapy may be reduced. Finally, although less predictive of the likelihood of complications, patient selection remains an important consideration, particularly in the choice of 2 procedures of apparently equivalent efficacy in elderly patients or those with overt peripheral vascular disease.

Study limitations: The relatively small number of access site complications in this study limits the number of clinical and procedural variables that can be legitimately evaluated as predictive factors. Similarly, the low event rate does not permit any direct comparison of the likelihood of complications after the respective coronary interventional procedures. Finally, multivariable regression analysis was not performed; the variables identified by univariate analysis may thus be interrelated.

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Results of Coronary Angioplasty of Chronic Total Occlusions (the National Heart, Lung, and Blood Institute 1985–1986 Percutaneous Transluminal Angioplasty Registry)

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There has been increasing application of coronary angioplasty to patients with chronic total occlusions. The acute and long-term outcome in 271 patients after coronary angioplasty (142 single and 129 multiple stenoses) of a total occlusion was compared with 1,429 patients undergoing angioplasty of subtotal (≤99% stenosis) occlusions (885 single and 544 multilesion) participating in the 1985–1986 National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. Baseline characteristics were similar for each lesion group except for a higher incidence of prior myocardial infarction and left ventricular dysfunction (ejection fraction <50%) in patients with total occlusion. Major complications (death, myocardial infarction or emergency bypass surgery) were similar (p = not significant) between patients with total and subtotal occlusions for single (6 vs 7%) and multilesion angioplasty (9 vs 6%).

At 2 years, after making adjustments for baseline variables, patients with a total occlusion had a significantly increased risk of death compared with those with subtotal occlusion. There were no significant differences in cumulative event rates for myocardial infarction or bypass surgery. Approximately three-fourths of patients in each group were free of angina at 2 years. In conclusion, angioplasty of chronic total occlusions is associated with a similar acute complication rate. Despite similar relief of anginal symptoms, patients in the total occlusion group have a higher 2-year mortality.

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Percutaneous transluminal coronary angioplasty (PTCA) has become a well-established means of revascularization. With recent technologic developments and increased operator experience the primary success rate in 2 large series is approximately 90%.[1,2] This success rate represents pooled data from a heterogeneous population of patients. Patients undergoing angioplasty of a total occlusion represent a group in which the primary success rate is comparatively poor at approximately 50 to 72% depending on the definition and duration of total occlusion.[1,3–6] Despite this relatively low initial success rate, patients with total occlusions represent an increasing proportion of patients selected for angioplasty.[1] One of the reasons for this trend is that, theoretically, angioplasty of a chronic total occlusion can be attempted with little risk to the patient, i.e., it is hard to make a total occlusion worse and the vessel is frequently protected by collateral vessels. This theory is supported by previous studies.[5–7] However, the potential for serious complications during angioplasty of total occlusions has been well documented.[4,8–10] Accordingly, we sought to test the hypothesis that angioplasty of chronic total occlusions can be attempted with a lower complication rate than angioplasty of subtotal occlusions. Because previous reports have suggested a less favorable long-term outcome of total occlusions in patients after angioplasty, we also analyzed the clinical status of these patients at 2 years. To accomplish this, we compared the incidence of acute complications and the long-term outcome of 271 patients who underwent PTCA of at least 1 total occlusion with 1,429 patients undergoing PTCA of subtotal occlusions from the most recent National Heart, Lung, and Blood Institute PTCA registry.

METHODS

Patient population: The study population included patients undergoing their first angioplasty enrolled in the 1985–1986 Percutaneous Transluminal Coronary Angioplasty Registry of the National Heart, Lung, and Blood Institute.[1] Of the 1,801 Registry patients without myocardial infarction in the 10 days before angioplasty, we excluded 98 patients who had angioplasty attempted in a bypass graft or left main artery, or both, and an additional 3 patients whose procedure was stopped before angioplasty was attempted. Thus, of the remaining 1,700 patients, there were 271 patients who had angioplasty attempted of at least 1 total occlusion: 142 pa-

TABLE I Baseline Characteristics of Patients Undergoing Coronary Angioplasty of Total and Subtotal Occlusions

Characteristic	Single Stenosis			Multiple Stenoses		
	TO (n = 142) No. (%)	STO (n = 885) No. (%)	p Value	TO (n = 129) No. (%)	STO (n = 544) No. (%)	p Value
Demographic						
Mean age (years)	56.4	57.4	—	56.6	58.2	—
Age ≥ 65 years	35 (25)	225 (25)	—	36 (28)	154 (28)	—
Women	36 (25)	248 (28)	—	29 (23)	135 (25)	—
Baseline medical						
Unstable angina	77 (54)	420 (48)	—	60 (47)	246 (45)	—
Mean duration of symptoms (mos)*	2.1	2.6	—	2.2	2.8	—
Ejection fraction < 50%*	30 (24)	102 (15)	< 0.05	38 (35)	69 (16)	< 0.001
Multivessel disease	55 (39)	324 (37)	—	105 (81)	388 (71)	—
Medical history						
Prior myocardial infarction	64 (45)	279 (32)	< 0.01	88 (68)	173 (32)	< 0.001
Prior CABG	1 (1)	78 (9)	< 0.001	13 (10)	42 (8)	—
History of CHF*	2 (2)	43 (5)	—	13 (10)	33 (6)	—
History of DM*	20 (14)	114 (13)	—	17 (13)	76 (14)	—
History of SH*	60 (43)	397 (45)	—	58 (45)	275 (51)	—
Currently smoking*	40 (29)	270 (32)	—	40 (32)	145 (28)	—

*Some patients have missing values for these characteristics. The percentages given are those of patients with known data.
CABG = coronary artery bypass grafting; CHF = congestive heart failure; DM = diabetes mellitus; SH = systemic hypertension; STO = subtotal occlusion; TO = total occlusion.

tients underwent single lesion and 129 patients underwent multilesion angioplasty, 14 of whom had 2 total occlusions attempted. There were 1,429 patients who underwent attempted angioplasty of 1 or more subtotal occlusions (885 single lesion and 544 multilesion; mean stenosis 80.3%). Baseline characteristics of the study patients are detailed in Table I.

Definitions: Total occlusion was defined as 100% luminal diameter stenosis without any anterograde blood flow. Lesions that had ≤99% luminal narrowing with any anterograde flow, equivalent to ≥ grade 1 of Thrombolysis in Myocardial Infarction study, were defined as subtotally occluded. Coronary dissection was considered a complication if it resulted in major luminal narrowing precipitating a myocardial infarction, emergency coronary bypass surgery or termination of the procedure without a successful result. Abrupt closure was considered to occur only after the angioplasty was considered complete. Vessel disease was classified as single, double or triple according to the definition of the Coronary Artery Surgery Study.[11] Acute clinical success was defined as all attempted lesions successfully dilated ≥20% with a residual stenosis <50%, without death, emergency coronary bypass surgery or myocardial infarction. Myocardial infarction was defined as the presence of 2 of the following: chest pain, serum creatine kinase increased to ≥1.5 times normal with positive MB fraction or presence of new Q waves. The category of "other complications" includes coronary spasm, branch occlusion, dissection, ventricular fibrillation and prolonged angina. The Canadian Cardiovascular Society classification was used to define anginal class. Unstable angina specifically referred to new chest pain that developed within the last 2 months, new chest pain at rest or with minimal effort, or other significant, unexplained changes in anginal pattern as defined in the Coronary Artery Surgery Study.[11] Long-term clinical success, determined at 2 years after angioplasty, was defined as no angina or angina improved over baseline without occurrence of death, myocardial infarction or coronary artery bypass surgery.

Estimated duration of the total occlusion was based on the date of the last prior infarction or the onset of the present level of symptoms in patients without prior infarction. No value for this variable was assigned to asymptomatic patients without prior infarction.

Statistical analysis: Comparisons between patient groups with angioplasty of total occlusions versus subtotal occlusions were performed according to whether patients underwent single or multilesion angioplasty. Differences in proportions between groups were assessed by chi-squared statistics of Fisher's exact test when the patient number for a subgroup was small. Differences in the distribution of normally distributed continuous variables were compared by Student's *t* test and by the Mann-Whitney nonparametric test for non-normally distributed factors. Cumulative event rate curves between groups were compared by the Mantel-Cox test. A multivariate logistic regression model incorporating variables before PTCA was developed to identify baseline variables predictive of acute and long-term success in patients undergoing PTCA of a total occlusion. The Cox porportional hazards model was used to assess risk of events over time in subgroups, and to adjust for the effect of covariates on this risk.

RESULTS

Baseline clinical characteristics: Baseline clinical characteristics for patients undergoing single and multilesion angioplasty of 1 or more total occlusions versus those with subtotally occluded lesions only are listed in Table I. Compared to the group with subtotal occlusion,

TABLE II Acute Outcome and Complications During Angioplasty of Total Occlusions Versus Subtotal Occlusions in Patients Undergoing Single and Multilesion Angioplasty

	Single Stenosis		Multiple Stenoses	
	TO (n = 142)	STO (n = 885)	TO (n = 129)	STO (n = 544)
	No. (%)	No. (%)	No. (%)	No. (%)
Angiographic outcome				
All stenoses dilated ≥20%	91 (64)*	793 (90)	77 (60)*	437 (80)
At least 1 stenosis dilated ≥20%	—	—	126 (98)	534 (98)
Clinical success				
All stenoses dilated ≥20%; no death/MI/Em. CABG	86 (61)*	760 (86)	74 (57)*	414 (76)
Major complications				
In-hospital death	3 (2)	6 (1)	2 (2)	4 (1)
MI	2 (1)	41 (5)	8 (6)	28 (5)
Emergency CABG	3 (2)	38 (4)	6 (5)	12 (2)
Death/MI/Em. CABG	8 (6)	64 (7)	11 (9)	35 (6)
Abrupt closure	5 (4)	14 (2)	3 (2)	14 (3)
Any complication†	35 (25)	180 (20)	35 (27)	123 (23)
Postangioplasty untoward events				
Heparin use ≥24 hours	19 (13)*	35 (4)	19 (15)	55 (10)
Elective CABG before Hosp. discharge	13 (9)*	16 (2)	1 (1)	9 (2)
Angina at discharge	16 (12)*	32 (4)	6 (5)	12 (2)

*p <0.001 versus STO.
†Defined as any major or other complication (see text).
Em. = emergency; Hosp. = hospital; MI = myocardial infarction; other abbreviations as in Table I.

patients undergoing angioplasty of a total occlusion were more likely to have had a prior myocardial infarction or a left ventricular ejection fraction <50%. The indications for angioplasty were similar in all 4 subgroups, with angina accounting for approximately 90% and recent infarction, asymptomatic coronary disease and undefined equally distributed among the other 10%.

Acute outcome and complications: Acute outcome and complications for patients undergoing single and multilesion angioplasty are listed in Table II. The likelihood of acute clinical success was lower in patients undergoing angioplasty of total occlusions compared to those with subtotal occlusions in both the single and multivessel cohorts.

The cumulative incidence of major complications (death, myocardial infarction or emergency bypass) was not significantly different for either single or multilesion angioplasty of total occlusions versus subtotal occlusions. Myocardial infarction occurred less often during single lesion angioplasty of a total occlusion than during angioplasty of a subtotal occlusion (1.4 vs 4.6%); however, this did not reach statistical significance (p = 0.12). Other complications occurred infrequently and were similar among all groups.

The likelihood of a major complication (death, myocardial infarction or emergency coronary artery bypass grafting) during an unsuccessful angioplasty was significantly less for attempted angioplasty of total occlusions (6%, n = 51) than for subtotal occlusions (34%, n = 92; p <0.001).

Patients undergoing single lesion angioplasty of a total occlusion were more likely to receive prolonged therapy with heparin (≥24 hours), require elective predischarge coronary artery bypass grafting or have angina on discharge (p <0.001 for all).

Lesion characteristics: Table III lists the lesion location and outcome for total and subtotal occlusions. Total occlusions were much more likely to receive col-

TABLE III Lesion Location, Outcome and Untoward Events in Totally Occluded Versus Subtotally Occluded Stenoses

	Total Occlusions (n = 285)	Subtotal Occlusions (n = 2,436)	
	No. (%)	No. (%)	p Value
Angiographic characteristics			
Coronary artery			
Right	128 (45)	702 (29)	<0.001
Left anterior descending	102 (36)	1,180 (48)	<0.001
Circumflex	55 (19)	553 (33)	—
Receives collaterals	249 (87)	308 (13)	<0.001
Outcome			
Stenosis reduced >20% and residual <50%	190 (67)	2,196 (90)	<0.001
Unable to pass stenosis	87 (31)	131 (5)	
Unable to pass wire	77	49	
Unable to pass balloon	8	69	
Other reason	2	13	
Unable to dilate*	8 (3)	108 (4)	
Final stenosis in successfully dilated lesions	29%	25%	<0.01
Untoward events			
In-lab occlusion	8 (3)	76 (3)	—
Out-of-lab abrupt reclosure†	8 (4.1)	36 (1.5)	<0.05
Coronary dissection‡	13 (5)	75 (3)	—

*Includes lesions with in-lab occlusion.
†Percentage expressed as proportion of successfully dilated lesions.
‡Dissection precipitating myocardial infarction, coronary bypass or termination of the procedure without a successful result.

lateral flow (87 vs 13%, p <0.001). Angiographic success was significantly lower for total occlusions (67%) compared with that for subtotal occlusions (90%, p <0.001). The most frequent reason for failure to dilate a total occlusion (accounting for 81% of the failures) was inability to pass a wire across the lesion. Although coronary dissection and occlusion in the laboratory were similar for both lesion types, the incidence of abrupt reclosure out of the laboratory appeared higher for successfully dilated total occlusions than for subtotal occlusions (4.1 vs 1.5%, p <0.05).

Multivariate predictors of acute clinical success: Independent baseline characteristics predictive of acute success were an estimated occlusion duration of <2 months, 1-vessel disease, and absence of angiographically detectable calcium in the occlusion (p <0.01, p <0.05 and p <0.05, respectively). No significant baseline variables predictive of acute success in those undergoing multilesion angioplasty were identified.

Long-term outcome: The cumulative 2-year rates for death and myocardial infarction after single and multilesion angioplasty are shown in Figure 1. Patients with attempted angioplasty of a single total occlusion had a nonsignificant trend toward higher mortality but less myocardial infarctions than those with attempted angioplasty of a subtotal occlusion. For patients undergoing multilesion angioplasty, the cumulative 2-year rates of death and myocardial infarction were similar.

The cumulative 2-year rates for coronary artery bypass grafting and repeat PTCA are displayed in Figure 2. For patients who underwent single lesion PTCA, there were no significant differences in the rate of bypass surgery between the groups with total and subtotal occlusions. In contrast, the rate of repeat angioplasty in the group with total occlusion was less than half of that in group with subtotal occlusion (8.2 vs 19.3%, p <0.002). The combined bypass surgery or repeat angioplasty rate, or both, was 25.2% for the group with total occlusion and 30.1% for the group with subtotal occlusion (p = not significant). In patients who underwent angioplasty of total and subtotal occlusion multilesions, rates were similar for coronary artery bypass grafting (15.7 vs 13.0%), repeat angioplasty (28.0 vs 25.3%) or either procedure (37.8 vs 34.8%).

The risk of death, myocardial infarction, bypass surgery and repeat angioplasty for the 2 years of follow-up was also evaluated after adjustments were made for the effects of age, gender, vessel disease, ejection fraction, congestive heart failure, diabetes, hypertension, unstable angina, prior infarction and prior bypass. Patients with total occlusion had a significantly increased risk of death in both the single lesion cohort (relative risk 4.39

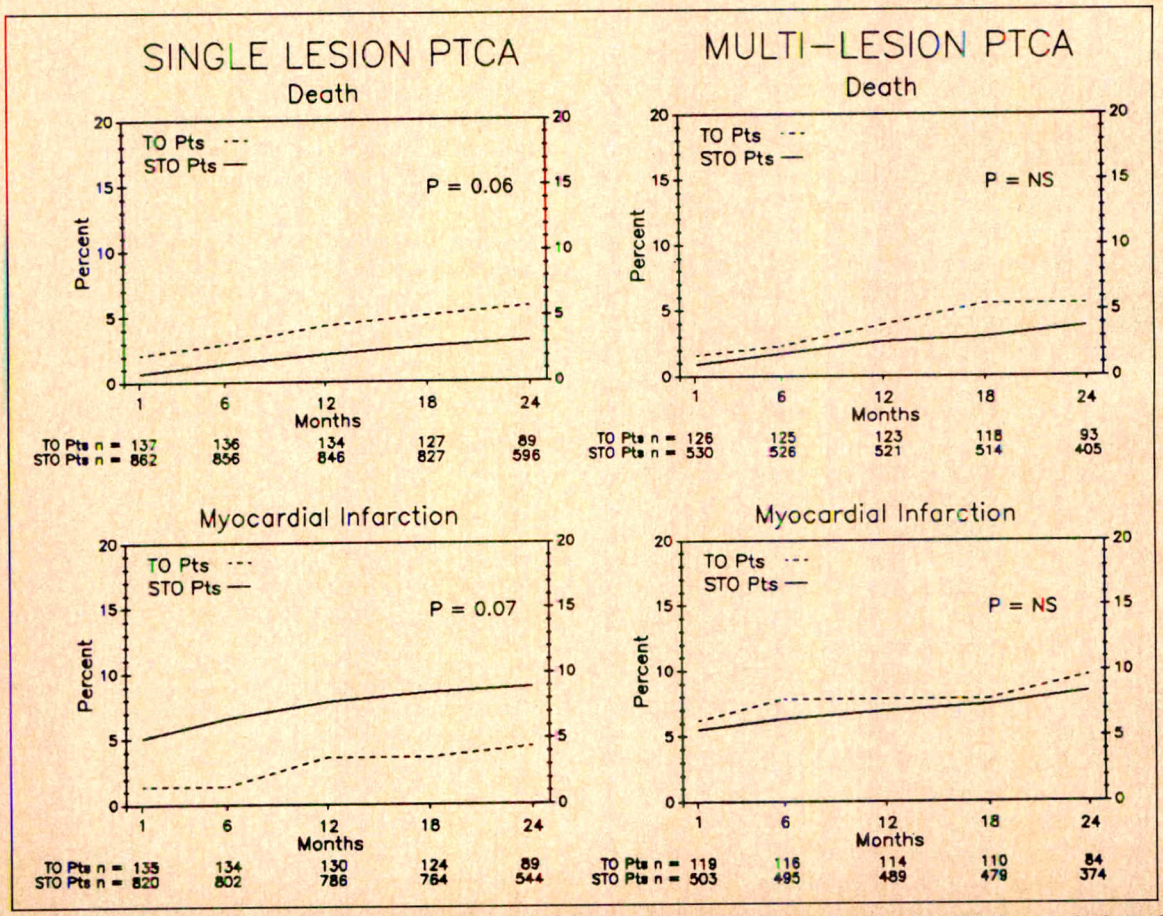


FIGURE 1. Cumulative 2-year rates for death and myocardial infarction in patients after single and multilesion angioplasty for a total occlusion versus subtotal occlusions only. The number of patients available for follow-up is present for each 6-month interval. NS = not significant; PTCA = percutaneous transluminal coronary angioplasty; TO Pts = patients with total occlusion; STO Pts = patients with subtotal occlusion.

[confidence interval 1.80, 10.74]) and multilesion cohort (relative risk 2.71 [confidence interval 1.05, 6.97]) compared to patients with subtotal occlusion. The effect of adjustments on outcomes other than death were not significant.

The anginal status of patients at 2 years is outlined in Table IV. Approximately three-fourths of patients were free of angina irrespective of having had single or multilesion angioplasty of either total or subtotal occlusions. Most of the patients with angina reported an improvement in their anginal symptoms compared with baseline. Use of antianginal medications was similar for all groups.

Long-term clinical success, as defined previously, was similar for total versus subtotal occlusion subgroups. For patients with single lesions, it was 72 vs 73%, and for those with multilesions, it was 74 vs 77%. When patients requiring repeat angioplasty during this period are included, the probability of success in all subgroups is reduced, particularly in patients with multilesions (65 vs 61% for patients with single lesions and 55 vs 58% for those with multilesions).

Multivariate predictors of long-term success: In patients with a single lesion who underwent angioplasty, the presence of 1-vessel disease ($p < 0.001$) and estimated occlusion duration of <2 months ($p < 0.01$) continued to be associated with a favorable outcome. In patients with a total occlusion who underwent multilesion angioplasty, the absence of congestive heart failure ($p < 0.01$), angina not unstable at the time of angioplasty ($p < 0.05$) and attempted total occlusion located in the right coronary artery ($p < 0.05$) were independent predictors of long-term success in the multivariate model.

DISCUSSION

The objectives of this study were twofold: (1) to assess the complication rate associated with angioplasty of total occlusions compared with subtotal occlusions, and (2) to compare the long-term follow-up of patients in each cohort. The results of this study do not support the hypothesis that angioplasty of totally occluded vessels is safer than angioplasty of subtotal occlusions. Our results demonstrate a similar incidence of major complications and other complications occurring during angioplasty of total and subtotal occlusions. Although these results are contrary to our hypothesis, clinical experience illustrates that angioplasty of a total occlusion can be associated with major complications despite the presence of collateral flow. Angioplasty of total occlusions has its own spectrum of complications including embolization of frequently associated thrombus, compromise of collateral vessels, particularly if they are bridging the obstruction, wire dissection secondary to the need for more steerable wires, and poorly understood reflow

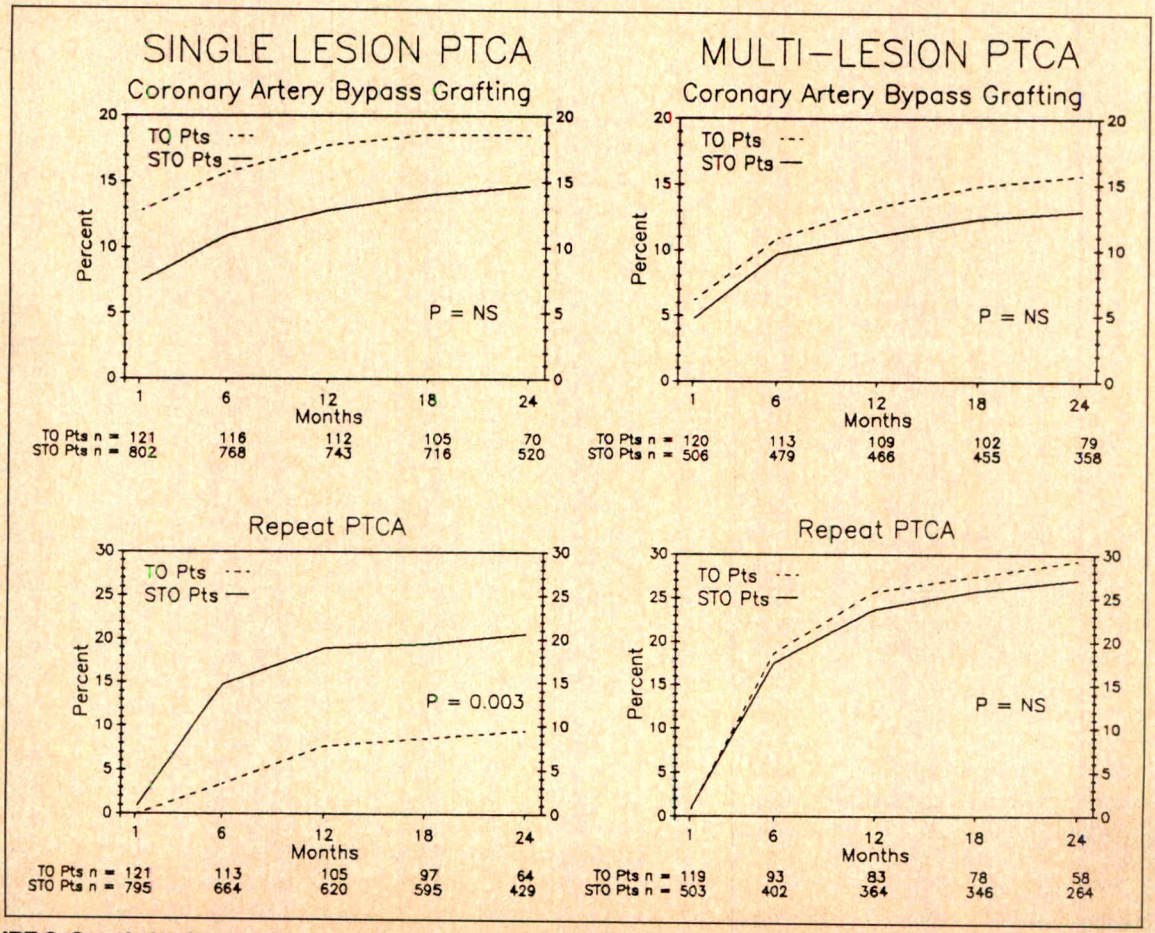


FIGURE 2. Cumulative 2-year rates for coronary artery bypass grafting and repeat angioplasty for total occlusion versus subtotal occlusions only. Abbreviations as in Figure 1.

TABLE IV Angina Characteristics at Two Years in Patients After Single and Multilesion Coronary Angioplasty of a Total Occlusion Versus Subtotal Occlusion Only

	Single Stenosis		Multiple Stenoses	
	TO (n = 142)	STO (n = 885)	TO (n = 129)	STO (n = 544)
	No. (%)	No. (%)	No. (%)	No. (%)
Angina status				
No angina	100 (80)	621 (76)	86 (73)	408 (80)
Angina	25 (20)	198 (24)	32 (27)	101 (20)
Improved	17 (14)	135 (16)	23 (19)	80 (16)
Same	6 (5)	47 (6)	6 (5)	12 (2)
Worse	1 (1)	14 (2)	2 (2)	3 (1)
Unknown	1 (1)	4 (1)	1 (1)	6 (1)
Patients with angina				
CCS I	9 (36)	60 (30)	13 (41)	33 (33)
CCS II	9 (36)	78 (39)	12 (38)	44 (44)
CCS III	6 (24)	27 (14)	3 (1)	10 (10)
CCS IV	1 (4)	10 (5)	2 (6)	—
CCS V (nonexertional)	—	13 (7)	1 (3)	7 (7)
Stable, unknown CCS	—	—	—	1 (1)
Unstable	—	10 (5)	1 (3)	6 (6)

CCS = Canadian Cardiovascular Society class; No. = patients alive and reporting data; other abbreviations as in Table I.

phenomena that are frequently associated with ischemia.[4,8–10] Although the nature of the complications may differ compared with angioplasty of subtotal occlusions, our analysis suggest that adverse outcomes occur at similar frequencies.

One finding that partially explains the perception that angioplasty of a total occlusion can be approached with greater safety is that one can fail without an adverse outcome much more frequently than with a subtotal occlusion. The incidence of a major complication with unsuccessful angioplasty of a total occlusion was only 6% compared with 34% for a subtotal occlusion. Thus, one can fail during attempted angioplasty of a total occlusion and only rarely experience a serious adverse outcome, whereas failure during angioplasty of a subtotal occlusion frequently results in an adverse outcome. Because failure occurs often with total occlusions and occasionally with subtotal occlusions, there is no difference in the overall complication rate.

The conclusion that complication rates are similar for both total and subtotal occlusions is in conflict with previous studies.[5–7] In the report by Melchior et al,[5] the lack of a cohort of patients with subtotal occlusions for comparison does not permit an assessment of risk. Nevertheless, complications in this study occurred with myocardial infarction in 2 patients and an episode of ventricular fibrillation in 3 of 100 patients with total occlusions. In the study by Safian et al,[7] the actual overall incidence of major complications was no different in patients with total, functional total and conventional stenoses. However, because there was no death or emergency surgery in the total occlusion group, these investigators concluded that many of the recognized hazards associated with angioplasty of total occlusions can be avoided by careful patient selection and technique.[7] In contrast, the study by Stone et al[6] demonstrated a lower incidence of bypass surgery and myocardial infarction but the same incidence of death in the groups with total and nontotal occlusions.

Multivariate analysis identified 3 factors that were predictive of acute success: estimated occlusion duration of <2 months, 1-vessel disease, and absence of calcium in the lesion. An inverse relation between duration of occlusion and likelihood of success has been reported in other series.[4,5,12] Multivessel disease and the presence of calcium have been associated with decreased success in analyses involving patients with subtotal occlusions but has not been previously noted for patients with total occlusions.[13,14]

Long-term outcome: Revascularization by angioplasty, as is true with bypass surgery, is performed primarily to relieve symptoms. Thus, it is reassuring that the long-term anginal status of patients after angioplasty of a total occlusion is comparable to patients undergoing angioplasty of subtotal occlusions. Most patients reported no angina or an improvement in their anginal status compared with baseline at 2 years and only a few had Canadian Cardiovascular Society class III or IV angina. These results confirm and expand on previous studies that reported excellent short-term (mean follow-up 8 months) improvement of anginal symptoms after angioplasty of a total occlusion.[4,5] However, it is disturbing that the long-term risk of death is higher in patients with total occlusions than subtotal occlusions. The reason for this increased risk is not readily apparent since the usual determinants of long-term prognosis (i.e., age, ejection fraction, vessel disease, congestive heart failure) were adjusted for. A possible explanation is the degree of revascularization after angioplasty. Because the success rate is lower in the group with total occlusion, they must have had more incomplete revascularization than the subtotal group. This is true even after factoring in subsequent bypass surgery, which was comparable in the 2 groups. It is also known that patients with a total occlusion have an increased risk of late, and often silent, restenosis.[3,5,7,15,16] Thus, although the degree of revascularization obtained or the presence of existing collateral vessels is adequate to relieve symptoms in most patients with total occlusion, they may not be adequate in preventing death in the event of further disease progression. This hypothesis is supported by the several-fold higher 2-year mortality rate in the cohort with single lesion total occlusion in whom angioplasty had failed versus those in whom it was successful (14.3 vs 1.2%). The 14.3% mortality is nearly threefold higher than mortality in the comparable group with subtotal occlusion (5.6%). The explanation may also be more complicated and involve lesion factors and aggressive disease progression, which predispose these patients to develop complete occlusions rather than more gradually progressive subtotal occlusions.

Study limitations: A limitation of this study is the lack of angiographic follow-up. Clearly, it would be of interest to correlate the relation of vessel patency and left ventricular function with clinical outcome. This is especially true since previous studies suggest a very high

restenosis and reocclusion rate in patients with total occlusions.

Multiple variables were examined and therefore some spurious associations may have been detected. However, we have tried to emphasize only those associations that have clinical importance, are very strong (those with $p < 0.001$), and persist even when patients are divided into subgroups. Our ability to detect a true difference in the incidence of complications — assuming a 5% event rate in 1 group — is 78% for a 5% difference and >99% for a 10% difference for our overall study.

This study analyzes the outcome of patients in whom angioplasty was performed in 1985 to 1986. Although angioplasty catheters and wires have been improved significantly since then, with the exception of a few research centers, the approach to angioplasty of a total occlusion has not changed significantly. The limiting step is still passing the wire through the total occlusion. Advances in wire technology have made the tips softer and less traumatic but also less likely to cross a total occlusion. Steerable wires are often required during PTCA of total occlusions and their design has not changed significantly. Perhaps angioplasty of subtotal occlusions has become safer, reinforcing the conclusion that PTCA of total occlusions has similar risk to subtotal occlusions.

Clinical implications: The frequency of patients with chronic total occlusions undergoing angioplasty has increased in recent years. Our findings suggest that angioplasty in this group of patients, compared to those with subtotal occlusions, is a reasonable approach based on comparable improvement in anginal status. Factors such as occlusion duration <2 months, 1-vessel disease and absence of calcium appear predictive of long-term success and thus can be used to help in patient selection. However, one must recognize that despite comparable improvement in symptomatology, this group of patients has a higher mortality at 2 years than patients who present with subtotal occlusions. This long-term mortality appears to be concentrated in the subgroup of patients with total occlusion having an unsuccessful result and may be secondary to incomplete revascularization. Perhaps more aggressive referral for bypass surgery after unsuccessful angioplasty would improve their long-term mortality; further investigation in this area needs to be done.

Contrary to previous studies, our analysis of a large group of patients with total occlusion demonstrates an incidence of acute complications similar to that seen in patients with subtotal occlusions. Since the likelihood of clinical improvement is also similar, this should not be a deterrent in accepting a patient for angioplasty. However, angioplasty of total occlusions is not without risk, and the same precautionary measures used during PTCA of subtotal occlusions, such as surgical backup, should be exercised.

APPENDIX

The following persons and institutions participated in the National Heart, Lung, and Blood Institute's 1985–1986 Percutaneous Transluminal Coronary Angioplasty Registry.

Clinical centers: Boston University Medical Center/University Hospital (Boston): David P. Faxon, MD,* Mirle A. Kellett, MD† (former), Timothy Sanborn, MD† (former), Alice K. Jacobs, MD,† Madeline Erario‡; Emory University Hospital (Atlanta) (because data from this center are currently being integrated into the new-registry data base, this site was not included in the analysis): Spencer B. King III, MD,* John Douglas, MD,† and Cynthia Sutor‡; Georgetown University Hospital (Washington D.C.): Kenneth M. Kent, MD,* Carolyn Ewels,‡ and Katie Kehoe†; Massachusetts General Hospital (Boston): Peter C. Block, MD,* and Elizabeth Block‡; Mayo Clinic (Rochester, Minn.): David R. Holmes, Jr., MD,* Ronald E. Vlietstra, MD,† Guy S. Reeder, MD,† J.F. Bresnahan, MD,† D.R. Bresnahan, MD,† A.A. Bove, MD,† LaVon Hammes,‡ and Susy Brevig‡; Medical Center Hospital (Houston): Mahdi Al-Bassem, MD,* and Debbie Lance‡; Medical College of Pennsylvania (Philadelphia): Lamberto G. Bentivoglio, MS, MD,* and Eileen Shappell‡; Medical College of Virginia (Richmond, Va.): Michael J. Cowley, MD,* George W. Vetrovec, MD,* Stephen A. Lewis, MD,† Germano DiSciascio, MD,† and Kim Kelly‡; Miami Heart Institute (Miami, Fla.): Arthur J. Gosselin, MD,* Paul S. Swaye, MD,† Paul A. Vignola, MD,† and Hazel Yon†; Montreal Heart Institute (Montreal): Martial G. Bourassa, MD,* Paul Robert David, MD* (former), Micheline Labbe‡, and Claudette Faille‡; National Heart, Lung, and Blood Institute (Bethesda, Md.): Richard O. Cannon, MD,* Martin Leon, MD,* and Rita Mincemoyer†; Seton Medical Center (Daly City, Calif.): Richard K. Myler, MD,* Simon H. Stertzer, MD,* David A. Clark, MD,* Mary Murphy‡; Rhode Island Hospital/Brown University (Providence, R.I.): David O. Williams, MD,* and Shirley Emin‡; St. Francis Regional Medical Center (Wichita, Kans.): Joseph P. Galichia, MD,* and Jan Meires‡; St. Luke's Episcopal Hospital (Houston): Louis L. Leatherman, MD,* Arthur J. Springer, MD,† and Joan Matties‡; St. Luke's Hospital (Milwaukee): Gerald Dorros, MD,* Lynne Janke-Mathiak,‡ and Marla Engel.

Data coordinating center: University of Pittsburgh (Pittsburgh): Katherine M. Detre, MD, DrPH,* Sheryl F. Kelsey, PhD,* John Wilson, PhD, Richard Holubkov, MS, Anne Rodwald Steenkiste, MS (statisticians); William Amoroso (manager systems analysis); Harriet Elliott (programmer); Verna Neidermeyer (data manager); Polly Swanson and Jayne Zona (research assistants); Donna Gibbons (administrative secretary), and Rita Wolk (secretary).

National Heart, Lung, and Blood Institute: (Bethesda, MD) Thomas Robertson, MD (program office).

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Establishing Comprehensive, Quantitative Criteria for Detection of Restenosis and Remodeling After Percutaneous Transluminal Coronary Angioplasty

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To establish comprehensive criteria for detecting restenosis and remodeling, inter- and intraobserver reproducibility of quantitative arteriography in the analysis of 20 lesions immediately after and 6 months after percutaneous transluminal coronary angioplasty (PTCA) were assessed. Geometric single-plane (minimum, maximum, mean diameter and percent diameter stenosis), biplane (absolute and relative cross-sectional area stenosis), relative densitometric area stenosis and the average of densitometric area stenosis in orthogonal views were compared. A high intra- and interobserver reproducibility of all absolute measurements was found, with the highest correlations for minimum diameter and cross-sectional area (interobserver, r = 0.85 and 0.85; intraobserver, r = 0.93, and 0.95 for minimum diameter and cross-sectional area, respectively). Of the relative measurements, biplane geometric percent cross-sectional area stenosis was the most reliable and percent densitometric area stenosis was the most variable (interobserver, r = 0.67; intraobserver, r = 0.71). Only small differences were demonstrated for the absolute measurements between the analysis of lesions immediately after PTCA and after follow-up, whereas a greater variability was found for relative measurements, especially videodensitometry. In both circumstances, a poor correlation between relative densitometric cross-sectional area from orthogonal views was found, whereas geometric elliptical cross-sectional area correlated quite well with the average of densitometric percent cross-sectional area in orthogonal views (interobserver, r = 0.86; intraobserver, r = 0.84). Thus, data in this study support the suitability of geometric quantitative analysis for the assessment of PTCA results. Densitometry was the least reliable quantitative parameter.

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Visual estimation of coronary stenosis severity is highly variable and unreliable.[1–3] In an attempt to overcome these limitations, computerized quantitative coronary arteriographic analyses have been described and shown to decrease the amount of observer variability.[4–6] Quantitative coronary arteriographic methods can be classified as geometric or densitometric. The former are based on the analysis of the geometric diameter of the artery as it is projected onto the intensifier and yield absolute and relative values of cross-sectional area, assuming circular (for single-plane analysis) or elliptical (for biplane analysis) cross-sectional shape of the artery.[4–6] Videodensitometry methods are based on the concept that the integral of density values across an artery in a radiographic image is proportional to the cross-sectional area at that point and can be used to derive percent area stenosis by comparing the density profile across a normal segment with that across a stenotic segment.[7–9] Theoretically, this should make the measurements of asymmetric stenoses independent of the projection angle and allow more accurate description of complex lesions with irregular cross-sectional shape.

Interventional techniques, which have become widely used in this last decade, require precise and accurate methods in the evaluation of coronary stenosis dimensions. Moreover, because percutaneous transluminal coronary angioplasty (PTCA) can often produce asymmetric and irregular changes of the vessel lumen, densitometric analysis has been proposed to assess PTCA results.[10] In these circumstances it has been suggested that geometric assumptions would prevent an accurate and reproducible evaluation of vessel dimensions. On the other hand, a lack of correlation between densitometric measurements in orthogonal views before and after PTCA has been reported.[11] Also Katritsis et al[12] demonstrated difficulties with videodensitometry, specifically in evaluation of PTCA results.

The purposes of this study were: (1) to compare the reproducibility of geometric and densitometric quantitative analysis in the assessment of the results of coronary intervention; (2) to evaluate the differences in accuracy and precision for both techniques in the analysis of stenoses immediately after PTCA and of the same lesions after a follow-up of 6 months; and (3) to establish comprehensive, quantitative criteria for the assessment of restenosis and remodeling after coronary interventions.

METHODS

The geometric and densitometric quantitative analysis of 20 lesions immediately after PTCA and after a follow-up of 6 months in 15 consecutive patient studies performed by 2 observers were compared. PTCA was performed on the left anterior descending artery in 10, on the circumflex in 3, on the obtuse marginal in 4 and on the right coronary artery in 3 cases. Lesions were not preselected on the basis of the location, geometry or ease of computer processing. The only requirement was availability of multiple views, so that a biplane analysis could be performed. The 2 observers analyzed all the lesions twice, independently, immediately after PTCA and after follow-up, with an interval of at least 1 week between the first and the second analysis. The results were then compared with those of a single, long-time user of the software who analyzed all 20 lesions independently and whose results were considered the reference standard for the study. Each of the users had been trained in the use of the software program and the conventions of cineframe selection and digitization used in this laboratory[6] as well as the Coronary Artery Surgery Study site code.[13] Choice of the frame, details of digitization, editing of edges and selection of normal reference diameters were completely up to the user's discretion. Only the location of PTCA lesions was given to the observers. Each lesion was analyzed in roughly orthogonal right anterior oblique and left anterior oblique projections. Comparable views were selected for both post-PTCA and follow-up analyses. The 20 biplane lesions analyzed immediately after PTCA and at 6 months necessitated digitization of $20 \times 2 \times 2 = 80$ cineframes for each set of observations. Since the long-time user performed this analysis once and the 2 users did this each twice, 400 cineframes were analyzed for this study.

The imaging procedure and quantification software have been described previously.[6] Selected frames were projected on a Vanguard viewer optically coupled to a video camera. With a 2.4:1 optical magnification, the subregions of the 35 mm frame of interest were digitized at $512 \times 512 \times 8$ bit resolution on a digital angiographic computer system (DPS-4100C, ADAC Laboratories, Milpitas, California). To reduce the video noise, 25 video frames were averaged.[14] All images were subjected to a gray-scale modification to linearly expand their individual scene dynamic range to fill the full 8 bit dynamic range of the digital radiographic system. The digitized film images were digitally magnified by a factor of 2, through bilinear pixel interpolation, to increase analytic precision in the analysis. Thus, the final overall magnification was ×4.8 and the effective pixel resolution was $2,458 \times 2,458$. The operator selected a circular region of interest with a light-pen cursor and modified the radius of the circle to include the stenotic and the "normal" reference segments. The software then proceeded without operator interaction. The centerline of the arterial segment was determined by analyzing circular pixel density profiles of decreasing radii. Linear density profiles perpendicular to the centerline were then extracted over the entire length of the arterial segment. Automatic edge detection was accomplished in 2 passes. On the first pass, initial edge points were chosen as points 75% of the distance between the first and the second derivatives (weighted toward the first derivative) of each perpendicular density profile. During this first pass, incorrect edge points were sometimes generated because of image noise, insufficient contrast or overlying structures. Edge points were automatically checked for spatial continuity and discarded if they were >4 pixels distant from neighboring edge points. Threshold density values for valid first-pass edge points were stored for later reference. In the second pass, thresholds for discarded points were calculated using thresholds of adjacent points. Calibration was obtained by measuring the catheter of known size, filled by contrast medium, and determining its edges in the same manner as the arterial segment. After analysis of the lesion in both orthogonal views was completed, the program automatically identified a proximal and distal normal segment and the point of minimum diameter. Automatic selection of proximal and distal segments was accomplished by searching out from the minimum diameter in both directions and finding the point where the artery diameter exceeded 90% of the difference between the maximum and minimum diameter for that segment. The user had the option to overrule this automatic selection. The final computer results consisted of the geometric minimum diameter, percent diameter stenosis for single-plane analysis, geometric percent area stenosis, and the absolute cross-sectional area assuming an elliptical cross-sectional shape for biplane analysis. In 2 cases, in which an ectatic portion of artery was included in the region of interest, the "normal" reference segment was manually redefined by the operators. Since Ellis et al[15] had suggested that mean diameter might be the most reliable parameter to quantitate progression of coronary lesions, we also calculated mean and maximum diameters of the segments — automatically and manually determined, respectively — for each lesion in each orthogonal view.

A different portion of the program provided relative videodensitometric cross-sectional area at each point along the centerline by integrating the densities across the perpendicular profile from edge to edge. The edge points were used both as limits for the integration of the individual density profiles and to provide a measure of the typical background densities in this part of the image. Background was subtracted using the edge-point intensities to construct a linearly interpolated approximation for the superimposed background across each profile. For each lesion, videodensitometric percent area stenosis in both orthogonal views and the average of these values were recorded.

Statistical analysis: Student's paired *t* tests and linear regression analysis were performed for the comparison of stenoses as assessed in single and biplane geometric analysis and in single-plane densitometric analysis. Moreover, the mean difference ("accuracy"), the standard deviation of mean difference ("precision"), mean absolute difference (the average of the values of the dif-

ference between the 2 readings without concern as to the direction or sign of the difference ["accuracy" previously defined]) and percent absolute difference (the difference between measurements expressed as a percentage of the reference value) were also calculated. These were compared using a repeated-measures analysis of variance, and when overall significance was found, the Newman-Keul test was used to compare the individual parameters with each other. For comparisons that involved biplane observations versus single-plane observations, 2 identical biplane observations were used to correspond with each single-plane observation. A paired *t* test was used to compare percent biplane geometric cross-sectional area versus percent videodensitometric cross-sectional area stenosis averaged from orthogonal views, because they were the only statistically compared parameters with sample sizes of 40 (single-plane analyses have a sample size of 80). Results were considered significant at $p < 0.05$.

RESULTS

The inter- and intraobserver variability results did not differ between the 2 test observers and were therefore considered as 1 data set.

A high intra- and interobserver reproducibility was demonstrated for all the absolute measurements (Table I). With regard to relative measurements, percent diameter stenosis showed an excellent reproducibility (interobserver, r value = 0.86; intraobserver, r = 0.86). Biplane analysis further improved the results of relative geometric single-plane analysis as shown by the better value of r (percent cross-sectional area interobserver, r = 0.89; intraobserver, r = 0.93), accuracy (percent diameter stenosis: interobserver, −1.35; intraobserver, −0.73; percent cross-sectional area: interobserver, −1.16; intraobserver, −0.22) and precision (percent diameter stenosis: interobserver, 9.03; intraobserver, 8.1; percent cross-sectional area: interobserver, r = 8.21; intraobserver, 6.61). None of the accuracy values (mean deviations) were significantly different from zero. In contrast, inter- and intraobserver variability of densitometric area stenosis were quite poor, but by averaging the values obtained in orthogonal views, the reproducibility increased remarkably (interobserver, r = 0.74; intraobserver, r = 0.84; accuracy: interobserver, 1.20; intraobserver, 2.15; precision: interobserver, r = 15.00; intraobserver, r = 12.12; mean absolute difference: interobserver, 10.84; intraobserver, 8.57). However, these results were still worse than those noted with the geometric analyses.

To allow a comparison of the reproducibility of parameters with different dimensions and number of observations, we also calculated the percent absolute difference (Figures 1 and 2). Both inter- and intraobserver tests showed that mean diameter is the most reliable parameter. Single-plane relative measurements were less reproducible than absolute ones. Videodensitometric percent cross-sectional area was unreliable (interobserver 24.9%, intraobserver 24.5%). However, by averaging percent densitometric cross-sectional area in

TABLE I Overall Variability of Absolute Measurements

	Min. Diam. (mm) (n = 80)	Max. Diam. (mm) (n = 80)	Mean Diam. (mm) (n = 80)	CSA-G (mm^2) (n = 40)
Interobserver:				
Mean difference	0.04	0.14	0.07	0.15
SD of mean difference	0.41	0.81	0.49	1.21
Mean absolute difference	0.29	0.58	0.35	0.71
r Value	0.85	0.80	0.82	0.85
Intraobserver				
Mean difference	0.00	0.01	0.01	−0.09
SD of mean difference	0.31	0.55	0.36	0.83
Mean absolute difference	0.21	0.40	0.23	0.54
r Value	0.93	0.91	0.91	0.95
	%DS (n = 80)	%CSA-G (n = 40)	%CSA-V (n = 80)	%CSA-Vavg (n = 40)
Overall Variability of Relative Measurements				
Interobserver:				
Mean difference	−1.35	−1.16	1.20	1.20
SD of mean difference	9.03	8.21	18.18	15.00
Mean absolute difference	6.75	5.76	13.16	10.84
r Value	0.86	0.89	0.67	0.74
Intraobserver				
Mean difference	−0.73	−0.22	2.15	2.15
SD of mean difference	8.10	6.61	17.94	12.12
Mean absolute difference	5.94	5.52	12.83	8.57
r Value	0.86	0.93	0.71	0.84

CSA-G = geometric-elliptical cross-sectional area; %CSA-G = percent geometric-elliptical cross-sectional area; %CSA-V = percent videodensitometric cross-sectional area; %CSA-Vavg = percent videodensitometric cross-sectional area averaged from orthogonal views; Diam. = diameter; %DS = percent diameter stenosis; Max. = maximum; Min. = minimum; SD = standard deviation.

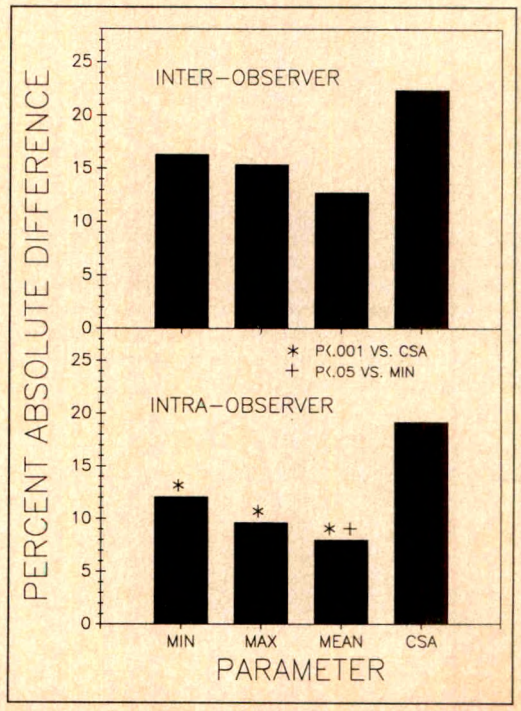


FIGURE 1. Percent absolute differences of the inter- and intraobserver results of minimum (min), maximum (max) and mean diameter, and of geometric elliptical cross-sectional area (CSA).

orthogonal views, a significant reduction of percent mean absolute difference was achieved (interobserver 19.7%, intraobserver 15.1%). In biplane analyses, the reproducibility of geometric relative measurements was excellent (interobserver 10.29, intraobserver 9.8).

An analysis was performed to determine the cut-off values of each measurement that could be used in practice to designate a true change in vessel dimensions (as might be caused by restenosis or remodeling of arterial segments) (Table II).

When the measurements obtained in the analysis of lesions 6 months after PTCA and after follow-up were considered separately (Tables III and IV), no relevant differences were demonstrated for both absolute and relative measurements. In both post-PTCA and follow-up films, the correlation between relative densitometric cross-sectional area from orthogonal views was poor ($r = 0.67$) (Figure 3). In contrast, a good correlation ($r = 0.85$) was found between geometric elliptical cross-sectional area and the average of percent densitometric cross-sectional area in orthogonal views. Accuracy, precision and mean absolute difference in the analysis of lesions immediately after PTCA and after follow-up are listed in Table V.

DISCUSSION

Several studies have shown that quantitative coronary angiography is superior to visual estimation in the

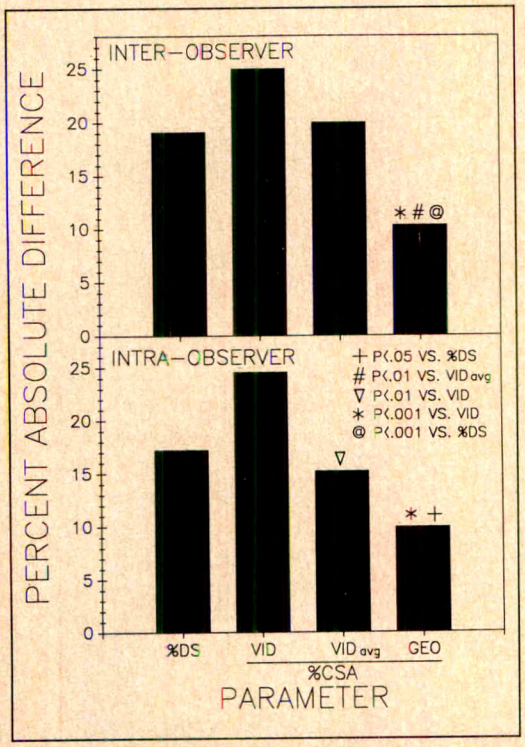


FIGURE 2. Percent absolute differences of the inter- and intraobserver results of the relative measurements. CSA = cross-sectional area; %DS = percent diameter stenosis; geo = percent geometric elliptical cross-sectional area stenosis; VID- = percent videodensitometric cross-sectional area stenosis; VIDavg = percent videodensitometric cross-sectional area stenosis averaged from orthogonal views.

TABLE II Summary of Cut-Off Values Proposed to Designate a Change in Vessel Dimensions (n = 80)

	Two Times Precision	
	Interobserver	Intraobserver
Min. diam. (mm)	0.82	0.62
Max. diam. (mm)	1.62	1.10
Mean. diam. (mm)	0.98	0.72
%DS	18.06	16.20
%CSA-G	16.42	13.22
%CSA-V	36.36	35.88
%CSA-Vavg	30.00	24.24

Abbreviations as in Table I.

TABLE III Variability of Absolute Measurements Immediately After PTCA and After Six Months Follow-Up

		Min Diam. (n = 40)	Max Diam. (n = 40)	Mean Diam. (n = 40)	CSA-G (n = 20)
Interobserver					
Mean difference	(I)	0.04	0.08	0.02	0.19
	(FU)	0.05	0.02	0.11	0.11
SD of mean difference	(I)	0.41	0.89	0.52	1.41
	(FU)	0.40	0.73	0.47	1.02
Mean absolute difference	(I)	0.29	0.61	0.37	0.75
	(FU)	0.28	0.55	0.32	0.68
r Value	(I)	0.84	0.80	0.83	0.83
	(FU)	0.84	0.82	0.83	0.85
Intraobserver					
Mean difference	(I)	−0.06	−0.13	−0.08	−0.23
	(FU)	0.05	0.15	0.09	0.06
SD of mean difference	(I)	0.25	0.46	0.33	0.85
	(FU)	0.35	0.60	0.38	0.81
Mean absolute difference	(I)	0.16	0.34	0.21	0.49
	(FU)	0.25	0.45	0.26	0.59
r Value	(I)	0.95	0.95	0.94	0.96
	(FU)	0.90	0.89	0.88	0.93

FU = follow-up; I = immediate; other abbreviations as in Tables I and II.

TABLE IV Variability of Relative Measurements Immediately after PTCA and After Six Months Follow-Up

		%DS (n = 40)	%CSA-G (n = 20)	%CSA-V (n = 40)	%CSA-Vavg (n = 20)
Interobserver					
Mean difference	(I)	−0.47	−0.57	2.80	2.80
	(FU)	−2.23	−1.75	−0.40	−0.40
SD mean difference	(I)	8.71	8.66	18.65	16.80
	(FU)	9.37	7.90	17.79	13.19
Mean absolute difference	(I)	6.17	6.18	13.72	12.35
	(FU)	7.33	5.35	12.61	9.33
r Value	(I)	0.78	0.82	0.52	0.56
	(FU)	0.88	0.92	0.75	0.83
Intraobserver					
Mean difference	(I)	0.47	0.34	1.96	1.96
	(FU)	−1.93	−0.78	2.35	2.35
SD mean difference	(I)	7.53	7.28	15.86	8.77
	(FU)	8.57	5.99	20.01	14.99
Mean absolute difference	(I)	6.08	6.28	12.49	7.13
	(FU)	5.80	4.75	13.17	10.01
r Value	(I)	0.84	0.87	0.70	0.88
	(FU)	0.91	0.96	0.70	0.80

Abbreviations as in Tables I to III.

assessment of the severity of coronary lesions. For this reason, quantitative coronary angiography has been largely used in research, whereas in the clinical setting traditional approaches are still widely used. However, a precise assessment of the stenosis severity can provide useful information about prognosis and may help to make therapeutic decisions.[16,17] Moreover, conclusions derived from studies in which coronary stenosis severity has been measured through quantitative coronary angiography may not be applied to visually estimated stenoses, because of the known differences between quantitative measurements and visual evaluations.[18,19] On the other hand, it has been suggested that frame and projection selection and other technical factors could decrease the reproducibility of quantitative coronary angiography, making such measurements unsuitable for clinical practice.

Inter- and intraobserver variability studies have often been performed after the selection of the frame to be analyzed, thereby yielding reproducibility values that may not be relevant to clinical use. In our study operators were given only the location of the stenosis to analyze after being trained in conventions used for quantitative analyses.[6] This freedom of analysis was intended to create a "worst-case" scenario similar to a clinical application of quantitative analyses. Nevertheless, under these conditions the reproducibility of geometric quantitative analysis was excellent.

In a previous study in which the same software was applied to preselected frames, interobserver r values of minimum diameter before and after PTCA were 0.95 compared with 0.84 in the current study (analysis of images before PTCA can be compared with that after follow-up). Therefore, the lack of preselection of the frame, although causing a decrease in reproducibility, does not preclude achievement of clinically reliable results. Moreover, the precision of minimum diameter showed in our study (interobserver, 0.61 mm; intraobserver, 0.31 mm) is comparable to that (0.36 mm) found by Reiber et al[20] in a highly structured research study. Thus, our data completely support the suitability of quantitative coronary angiography when differences in frame selection, reference selection and digitization parameters may differ from observer to observer — as might be expected in clinical practice.

The absolute measures provided by quantitative arteriography are attractive for assessing coronary interventions for several reasons. Studies in humans showed that minimal cross-sectional area can predict the hemodynamic significance of a coronary narrowing more accurately than percent area or percent diameter stenosis.[21] In addition, our results confirm previous reports[11,15] showing that absolute measurements are less variable than relative ones. We tested the reproducibility of maximum and mean diameters that theoretically could be used for the follow-up of vessels with no apparent lesions at the baseline or with diffuse disease. Ellis et al,[15] in a study confined to single-plane analyses, showed that mean diameter was the best parameter to assess the evolution of coronary lesions. Our data confirm that mean diameter is highly reproducible.

With respect to minimum diameter, we believe that the slightly greater value of the percent absolute difference can be justified by the smaller magnitude of this measurement (i.e., small differences in this measure-

TABLE V Variability Between Geometric and Videodensitometric (averaged) Cross-Sectional Area Stenosis

	Immediately After PTCA (n = 40)	Follow-Up (n = 40)	Overall (n = 80)
Interobserver			
Mean difference	1.6	1.8	1.7
SD of mean difference	10.4	10.7	10.5
Mean absolute difference	8.1	8.1	8.1
r Value	0.81	0.88	0.87
Intraobserver			
Mean difference	2.5	0.9	1.7
SD of mean difference	10.2	12.5	11.4
Mean absolute difference	8.2	9.4	8.8
r Value	0.81	0.85	0.85

PTCA = percutaneous transluminal coronary angioplasty; SD = standard deviation.

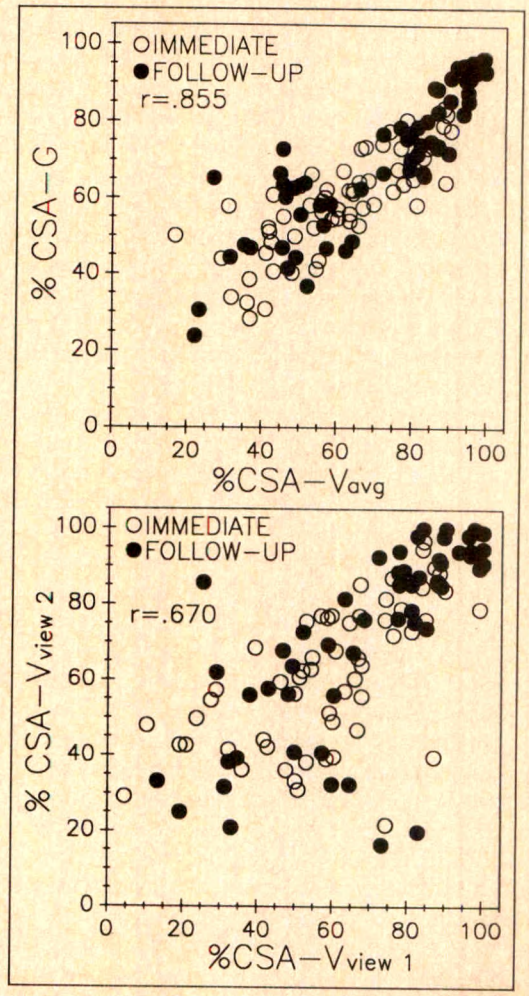


FIGURE 3. Linear regression analyses of percent geometric elliptical cross-sectional area (CSA-G) stenosis and percent videodesitometric cross-sectional area stenosis (CSA-V) averaged from orthogonal views *(upper panel)*, and of percent videodensitometric cross-sectional area stenosis from orthogonal views *(lower panel)* of lesions after percutaneous transluminal coronary angioplasty and follow-up.

ment will appear large when expressed as a percentage). The values of mean absolute difference (interobserver 0.29, intraobserver 0.21) were, in fact, excellent. The low value of mean absolute difference of geometric percent cross-sectional area relative to percent diameter stenosis may be a result of the same phenomenon (i.e., percent cross-sectional area measurements are more severe than percent diameter stenosis measurements because they are proportional to the radius squared). Thus, small differences in the latter would be proportionately larger when expressed as a percentage. We believe that the greater variability of stenosis cross-sectional area than that of minimum diameter can be explained by the fact that the former incorporates errors inherent in measuring minimum diameter in 2 views.

The applicability of geometric quantitative methods to evaluate results after PTCA has been controversial. It has been stressed that irregularities occurring after angioplasty cannot be accurately described by geometric assumptions of circular or elliptical models. Serruys et al[10] reported a good agreement between densitometric relative area and geometric single-plane percent stenosis before PTCA, whereas remarkable differences (standard deviation of the difference = 18% area stenosis) were recorded after PTCA. Because these results were interpreted as related to the complex anatomic changes of the vessel wall after PTCA that prevented a correct geometric analysis,[22] densitometry was proposed, instead of geometric quantitation, to evaluate PTCA results. Studies in phantoms have found that videodensitometry can accurately measure stenosis dimensions.[7–9] In contrast, our clinical data showed that variability of videodensitometry is greater than that of geometric methods when we consider inter- or intraobserver variability either after PTCA or after a 6-month follow-up period. Moreover these results confirm a poor correlation between densitometric relative area (r = 0.626 and 0.719 for intra- and interobserver test, respectively) in orthogonal views, as previously reported by other investigators.[11,12]

A nonlinear relation between film optical density and contrast medium thickness are caused by x-ray scatter, beam hardening, nonuniform brightness, effects of panning, inhomogeneous contrast mixing or foreshortening. Also, disparate gray-scaling methods may be used by different digital systems. These can explain the discrepancies between the results observed in the ideal conditions of phantom studies and those obtained in unselected clinical applications. Previous reports, which showed reliability of videodensitometry, were generally performed in highly selected, symmetric lesions[10] and without foreshortening,[8] characteristics that are common only among a minority of lesions. In contrast, in our study, no preselection of the stenoses was done and this could explain the differences between our results and the above-mentioned reports. In previous studies,[12] a lack of correlation between geometric and densitometric evaluation of percent area stenosis after PTCA was shown. Inhomogeneous mixing of contrast medium and blood due to the anatomic changes of the arterial wall immediately after PTCA could have caused these results because of violation of this fundamental prerequisite for performing videodensitometry. However, our videodensitometry results were highly variable both immediately and late after PTCA.

Although we found an improved reproducibility of videodensitometry when the values of orthogonal views were averaged and a good correlation between this mean and elliptical percent cross-sectional area, the results obtained through geometric analysis were always much more reproducible than those obtained through videodensitometry. We think that the poor reproducibility of videodensitometry, when applied to typical clinical studies, suggests that current approaches are not yet suitable for assessing angioplasty or other interventions.

Surprisingly, we did not observe a remarkable discrepancy in the analysis of post-PTCA and follow-up films, and this difference further diminished when biplane analysis was considered. These data support the concept that difficulties of geometric quantitative systems to describe the results of PTCA are less in practice than in theory. Biplane analysis, which has been proposed to overcome the problem of asymmetric lesions, has been shown to be highly reproducible with only small differences between immediate post-PTCA and follow-up analyses.

In conclusion, this study supports the suitability of geometric quantitative analysis for assessing coronary interventions in both research and clinical settings. Criteria are provided that allow the complete description of an arterial segment undergoing remodeling due to interventions. Of these criteria, densitometry, even when results from orthogonal views are averaged, is the least reliable. In our study, the differences in geometric analyses between post-PTCA and follow-up films were negligible, suggesting that geometric methods are most appropriate for assessing immediate and late PTCA results. Of these measurements, the mean and minimum diameter measurements are the most reliable.

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Comparison of Ischemic and Physiologic Responses During Exercise Tests in Men Using the Standard and Modified Bruce Protocols

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The importance of low-level (warm-up) exercise for reducing exercise-induced myocardial ischemic symptoms in patients with coronary artery disease is well-recognized by clinicians. Whether altering the abruptness of exercise, such as that which occurs during different frequently used testing protocols, affects myocardial ischemic variables and maximal exercise capacity has not been resolved. This study seeks to determine the effects of altering the increment of work-rate change per exercise stage on both the ischemic threshold and maximal exercise capacity using 2 frequently used exercise testing protocols. Thirty-two patients with documented coronary artery disease and previously positive exercise tests (ischemic ST depression ≥1.0 mm) performed symptom-limited exercise tests using both the standard and modified Bruce protocols in random order, 1 hour apart. Exercise electrocardiograms were analyzed to determine the ischemic threshold, defined as heart rate at onset of ≥1.0 mm ischemic ST depression.

Patients achieved a higher peak heart rate (124 ± 19 vs 117 ± 21 beats/min; p <0.0001), rate-pressure product (21.4 ± 3.9 vs 19.8 ± 4.1 beats/min × mm Hg × 10^3; p ≤0.0001) and oxygen consumption (VO_2) (18.5 ± 3.7 vs 16.5 ± 4.4 ml/kg/min; p ≤0.001) with the standard than with the modified Bruce protocol. At matched submaximal exercise stages there were no differences in VO_2, heart rate or oxygen pulse between protocols. Time to ischemic threshold was significantly reduced with the standard compared with the modified Bruce protocol (312 ± 107 vs 607 ± 221 seconds; p <0.0001). All other variables at the ischemic threshold were not significantly different between protocols, including heart rate, rate-pressure product, diastolic blood pressure and VO_2.

These data indicate that: (1) Myocardial ischemic threshold is the same with these 2 frequently used exercise testing protocols and is not altered by varying the work-rate increment between protocols. (2) Exercise capacity is greater with the standard than with the modified Bruce protocol, as patients achieved a higher peak heart rate, rate-pressure product and VO_2. (3) The physiologic responses at matched submaximal work rates are similar. Accordingly, ischemic and hemodynamic data obtained using these 2 protocols can be equivalently compared.

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Serial exercise testing is a frequently used and valuable method for assessing patients with coronary artery disease. Comparisons of exercise test data including hemodynamic, ischemic and exercise tolerance parameters are performed to evaluate changes in disease status and functional capacity over time. Serial exercise testing is also often used for the evaluation of patients after therapeutic interventions including percutaneous transluminal coronary angioplasty, coronary artery bypass surgery, pharmacological management and cardiac rehabilitative exercise programs. Usually, follow-up evaluations are performed using the same protocols, and a number of investigators have demonstrated high reproducibility of data using identical exercise protocols.[1–12] However, patients frequently perform serial exercise evaluations using different protocols for a variety of reasons, such as tests performed in a different hospital or by a different clinician, or both, or tests performed early (1 week) versus later (6 to 8 weeks) after myocardial infarction. There are few data to indicate whether ischemic and hemodynamic parameters can be equivalently compared when 2 possibly very different testing protocols are used.

The purpose of the present study was to compare the ischemic and physiologic responses during exercise when repeat exercise tests are performed on frequently used protocols that have different work-rate increments (namely, the standard and modified Bruce protocols).

METHODS

Patients: The study consisted of 32 men (mean age 59 ± 7 years) with documented, stable coronary artery disease evidenced by either a previous myocardial infarction, recent coronary angiography (≥70% arterial diameter narrowing of ≥1 major coronary artery) or positive thallium exercise test. They were chosen from a large cohort of patients undergoing exercise stress tests in our laboratory between April and August 1990. Most patients in this study (27 of 32) had recent history of classic exertional angina pectoris, with 33% having New York Heart Association class II or greater. All patients

had ≥1 recent positive exercise test using the criteria of ≥1.0 mm horizontal or downward sloping, or ≥1.5 mm upward sloping ST-segment depression at 0.08 second after the J point in 3 consecutive beats in ≥1 lead. Exercise-induced ST-segment depression may have been accompanied by chest pain characteristic of angina pectoris, but this was not a required inclusion criterion. Medical regimens at the time of testing included 21 patients on calcium antagonists (66%), 13 on β blockers (41%), and 6 on neither (19%).

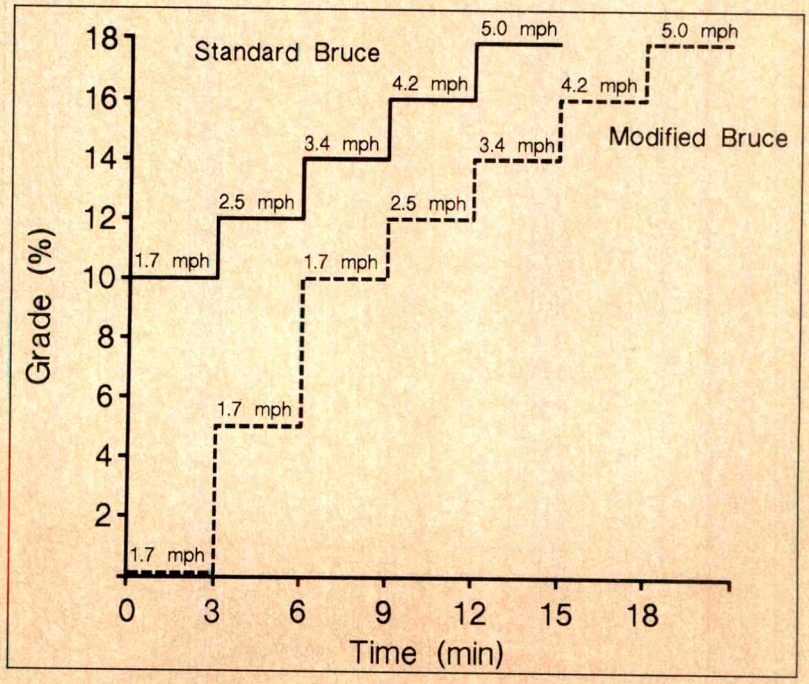
We excluded patients who had electrocardiographic changes at rest, including left bundle branch block, left ventricular hypertrophy with ST-segment strain pattern, horizontal or downward sloping ST-segment depression, or any significant arrhythmias. Patients were also excluded if they had known or suspected valvular disease, unstable angina pectoris or recent myocardial infarction (<3 months). Patients treated with digitalis glycosides were not included in the study, whereas patients receiving other cardiovascular medications maintained their usual treatment routine. Patients were advised to plan their medication administrations ≥1 hour before exercise testing. Patients were enrolled in the study after informed consent was obtained in accordance with the institutional review board for human research at University Hospital.

Exercise tests: All exercise tests were conducted at the exercise laboratory of University Hospital using a motorized treadmill, with the patients lightly gripping the handrails on the treadmill for support.

Testing protocols: Each patient performed a symptom-limited exercise test on both the standard and modified Bruce protocols (Figure 1) in a random order, with a 1-hour rest period between tests. The standard Bruce protocol[13] was chosen to represent abrupt exercise, because of the relatively large work-rate increments per stage and because of its wide clinical use for diagnostic and prognostic testing. The modified Bruce protocol[14] was chosen because of its similarity to the standard Bruce protocol except for an additional 6 minutes of low-level (warm-up) exercise that precedes Bruce stage I, and because it is a very frequently used low-level testing protocol. An equal number of patients (n = 16) performed the standard Bruce protocol first as performed the modified Bruce first. During the rest period, subjects were asked to refrain from eating or drinking beverages other than water, and remained seated in the exercise room. Before performance of the first exercise test, each patient performed a low-level walking trial for approximately 2 minutes to become familiar with the laboratory facilities and testing equipment, including the headgear apparatus that was used for measuring oxygen consumption (VO_2). Formal exercise testing was not begun until 15 minutes after heart rate and blood pressure returned to the previously determined levels at rest.

Auscultatory blood pressures and standard 12-lead electrocardiograms were obtained at rest, at 1 minute into each exercise stage, at onset of angina, at peak exercise, immediately after exercise, at 1 minute into recovery, and at 3-minute intervals during recovery until the return to baseline. To assure standardization of lead placement, subjects were required to keep all electrodes in place during the time intervals between tests. Heart rate was determined from direct measurement of the 12-lead electrocardiogram. Patients were asked to report any symptoms of chest discomfort and to rate pain that was typical of angina at its onset and during progressive exercise on a scale of 1 (mild) to 4 (severe).

Oxygen consumption: Total body VO_2 was determined directly by the method of oxygen and carbon dioxide gas analysis using a Sensormedics Horizon Metabolic Measurement Cart (Anaheim, California) that was calibrated before each exercise test with standard gas mixtures. Subjects had a nose clip in place and breathed room air through a 1-way directional valve



IGURE 1. Comparison of speed (mph) nd grade during each stage of standard ***olid line)*** **and modified** ***(dashed line)*** **ruce treadmill protocols.**

TABLE I Cardiopulmonary Values at Peak Exercise

	Standard Bruce	Modified Bruce	p Value
Heart rate (beats/min)	124 ± 19	117 ± 21	0.0001
Systolic blood pressure (mm Hg)	172 ± 16	168 ± 17	NS
Diastolic blood pressure (mm Hg)	77 ± 8	76 ± 9	NS
% Heart rate max	78 ± 11	74 ± 12	0.0001
Rate pressure product (beats/min × mm Hg × 10^3)	21.4 ± 3.9	19.8 ± 4.1	0.0001
Symptom-limited maximal oxygen consumption (ml/kg/min)	18.5 ± 3.7	16.5 ± 4.4	0.0001
Metabolic equivalent	5.3 ± 1.1	4.7 ± 1.3	0.0004

% Heart rate max = percentage of predicted maximal heart rate achieved; Metabolic equivalent = VO_2/3.5 ml/kg/min; NS = not significant.

system. VO_2 measurements (ml/kg/min) were obtained during each minute of each stage and at peak exercise.

Termination points: The exercise tests were terminated when any of the following occurred: horizontal or downward sloping ST-segment depression ≥3 mm; chest pain suspected as angina pectoris and rated as moderate (2 to 4); systolic blood pressure decrease of >10 mm Hg from levels at rest; >3 consecutive premature ventricular contractions; or fatigue such that the patient was unable to continue.

Ischemic threshold: Ischemic ST depression was defined as ≥1 mm horizontal or downward sloping or ≥1.5 mm upward sloping depression at 0.08 second after the J point in ≥3 consecutive complexes of the same lead. Heart rate and rate-pressure product at onset of ischemic ST-segment depression was defined as the ischemic threshold. The maximal amount of ST depression in any lead was measured. The interpretations of ischemic changes were performed by 1 experienced cardiologist who had no knowledge of the patient or of the exercise protocol used.

Submaximal exercise stages: Heart rate, blood pressures, VO_2 (ml/kg/min) and oxygen pulse (VO_2/heart rate) were determined at matched exercise stages during the standard and modified Bruce protocols for each patient. To assure steady state VO_2 values, the patient had to complete ≥2 minutes of exercise in a given matched exercise stage.

Analysis of data: Data are reported as mean ± standard deviation. Statistical comparisons of the individual subject data between protocols were performed using paired Student's *t* tests or chi-square evaluation. A value <0.05 was considered to be statistically significant.

RESULTS

Peak exercise variables: Sixty-four exercise tests (32 pairs using the standard and modified Bruce protocols) were performed. The tests were concordantly terminated in 30 patients (94%) for the following reasons: volitional fatigue (18 patients, 56%); onset of angina pectoris equal to a severity rating of 2 to 4 (6 patients, 19%); dyspnea (4 patients, 12%); and ischemic ST-segment depression >3 mm (2 patients, 6%). The termination points were discordant in 2 patients for whom the tests were stopped because of angina and ST-segment depression on the standard Bruce protocol and because of fatigue on the modified Bruce protocol. Mean time to symptom-limited maximal exercise was significantly greater ($p \leq 0.0001$) during the modified (698 ± 161 seconds) than during the standard (418 ± 112 seconds) Bruce exercise tests.

Peak exercise variables are listed in Table I. Mean peak heart rate was significantly greater ($p \leq 0.0001$) during the standard (124 ± 19 beats/min) than during the modified (117 ± 21 beats/min) Bruce exercise tests. A higher maximal heart rate occurred during the standard (24 patients, 75%) than during the modified Bruce protocol. Similarly, both the mean percentage of predicted maximal heart rate and the mean peak rate-pressure product were significantly greater ($p \leq 0.0001$) during the standard than during the modified Bruce

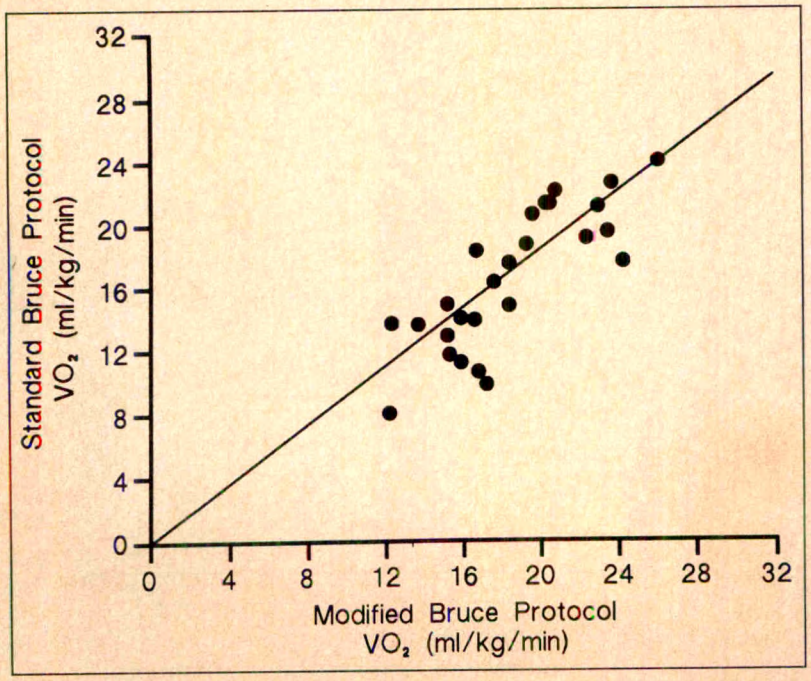


FIGURE 2. Plot of individual data points comparing peak oxygen consumption (VO_2) during paired standard and modified Bruce protocol exercise tests for each subject. *Solid line* represents line of identity.

TABLE II Comparison of Physiologic Variables at Matched Exercise Stages

	Standard Bruce	Modified Bruce	p Value
Stage I (1.7 mph/10% inclination) (n = 29)			
Heart rate (beats/min)	99 ± 12	101 ± 14	NS
Systolic blood pressure (mm Hg)	148 ± 17	151 ± 15	NS
Diastolic blood pressure (mm Hg)	78 ± 8	77 ± 9	NS
Rate-pressure product (beats/min × mm Hg × 10^3)	15 ± 3	15 ± 3	NS
Oxygen consumption (ml/kg/min)	13.5 ± 2.1	13.0 ± 3.0	NS
Oxygen pulse (ml/kg/beat)	13.6 ± 3.1 × 10^2	13.0 ± 4.0 × 10^2	NS
Stage II (2.5 mph/12% inclination) (n = 18)			
Heart rate (beats/min)	115 ± 17	115 ± 18	NS
Systolic blood pressure (mm Hg)	161 ± 17	160 ± 16	NS
Diastolic blood pressure (mm Hg)	78 ± 6	75 ± 7	NS
Rate-pressure product (beats/min × mm Hg × 10^3)	18 ± 3	18 ± 4	NS
Oxygen consumption (ml/kg/min)	17.5 ± 3.2	17.0 ± 3.8	NS
Oxygen pulse (ml/kg/beat)	15.8 ± 3.5 × 10^2	15.4 ± 4.1 × 10^2	NS

NS = not significant.

TABLE III Onset of Ischemic ST Depression During the Standard and Modified Bruce Protocols (n = 17)

	Standard Bruce	Modified Bruce	p Value
Time (s)	308 ± 105	596 ± 217	0.0001
Heart rate (beats/min)	122 ± 19	117 ± 21	NS
Systolic blood pressure (mm Hg)	164 ± 18	162 ± 18	NS
Diastolic blood pressure (mm Hg)	80 ± 7	78 ± 8	NS
Rate pressure product (beats/min × mm Hg × 10^3)	19.8 ± 3.9	18.9 ± 4.1	NS
VO_2 (ml/kg/min)	16.4 ± 3.5	15.8 ± 4.5	NS
Oxygen pulse (ml/kg/beat)	13.4 ± 1.8 × 10^2	13.5 ± 2.1 × 10^2	NS

NS = not significant; VO_2 = oxygen consumption.

TABLE IV Onset of Angina During the Standard and Modified Bruce Protocols (n = 11)

	Standard Bruce	Modified Bruce	p Value
Time (s)	311 ± 95	541 ± 160	0.0001
Heart rate (beats/min)	111 ± 16	105 ± 16	0.001
Systolic blood pressure (mm Hg)	163 ± 16	165 ± 18	NS
Diastolic blood pressure (mm Hg)	78 ± 10	78 ± 11	NS
Rate-pressure product (beats/min × mm Hg × 10^3)	18.1 ± 3.8	17.4 ± 3.5	NS
VO_2 (ml/kg/min)	16.7 ± 3.7	15.1 ± 4.3	0.01

NS = not significant; VO_2 = oxygen consumption.

protocol, with a higher rate-pressure product during the standard Bruce protocol occurring in 26 patients (81%).

Respiratory gas analysis was attempted in all subjects, but was successfully obtained in 26 (81%). VO_2 data for the remaining 6 subjects (19%) were not analyzed owing to technical difficulties. Mean VO_2 at peak exercise was significantly greater during the standard than during the modified Bruce exercise tests ($p \leq 0.0004$) with a higher peak VO_2 during the standard Bruce protocol occurring in 20 patients (77%) (Figure 2).

Submaximal exercise variables: There were no significant differences in mean heart rate, rate-pressure product, systolic or diastolic blood pressure, VO_2 or oxygen pulse determined at matched exercise stages for paired tests between the standard and modified Bruce protocols (Table II).

Exercise ischemic data: All exercise electrocardiograms were of interpretable quality. Twenty-six patients demonstrated ≥1 positive exercise test per pair of tests by the criterion of either ST-segment depression or angina pectoris. Twenty-one patients had 1 or both of the tests positive by the criterion of ST-segment depression, whereas 11 did not have ST depression during either test. Eleven patients had angina pectoris on both protocols, whereas 21 did not have angina on either protocol.

A chi-square analysis showed that there was no significant difference in the frequency of ischemic responses between tests using the 2 protocols. The maximal amplitude of ischemic ST-segment depression was also not significantly different between tests using the standard (2.2 ± 0.8 mm) and modified (2.0 ± 0.9 mm) Bruce protocols for the 17 patients who had concordantly positive tests.

Ischemic threshold: Tables III and IV list the variables at onset of ischemic ST depression and angina for concordantly positive test pairs. Mean time to onset of ischemic ST-segment depression was significantly greater ($p \leq 0.0001$) for the concordantly positive tests during the modified (607 ± 221 seconds) than during the standard (312 ± 107 seconds) Bruce exercise tests. Indexes of myocardial VO_2 (i.e., heart rate and rate-pressure product) were similar at the ischemic threshold during the standard and modified Bruce protocols (Figures 3 and 4). Systolic and diastolic blood pressures, VO_2 and oxygen pulse were also similar at the ischemic threshold during the tests using the 2 protocols. However, mean heart rate and VO_2 were significantly higher at the onset of angina during exercise on the standard than on the modified Bruce protocols.

DISCUSSION

Ischemic threshold: The findings of this study indicate that the additional 6 minutes of low-level exercise during the first 2 stages of the modified and standard Bruce protocols did not significantly alter the ischemic threshold. There was no difference in mean heart rate at ischemic ST depression for the 17 patients with concordantly positive tests by ST-segment depression on both protocols. The study patients were selected such that the ST-segment depression observed during the exercise

tests were true positive results. Eleven patients did not have ischemic ST-segment depression during tests using either protocol, despite the fact that 1 of the entry criteria for this study was a documented, recent positive exercise test by ischemic ST depression. This probably occurred because 7 of these patients reached a higher peak heart rate during earlier exercise testing and did not reach their ischemic threshold during tests performed for the present study. Five of these patients had a change in medical regimen before enrolling in this study. It is unclear why the 4 remaining subjects did not have an ischemic response in this study, because they were on the same medical regimen and achieved higher peak heart rates than they did on earlier tests.

In support of the findings of no significant "warm-up" effect causing a subsequent alteration in the ischemic threshold, mean diastolic blood pressures during the standard and modified Bruce protocols were not significantly different. Thus, any change in peripheral vasodilation causing variations in total peripheral resistance in the patients between protocols was not manifested. Had a significant difference in the mean diastolic blood pressures occurred, then an alteration in the ischemic threshold may have been expected, because these differences would also affect changes in coronary perfusion prsssures.

The importance of low-level (warm-up) exercise for reducing ischemic symptoms in patients with coronary heart disease is well-recognized by clinicians. However, there is a limited amount of research data available on the effects of altering the type of exercise on the ischemic threshold. Pupita et al[15] showed that the mean heart rate and rate-pressure product at 1 mm ST-segment depression was significantly higher when the modified Bruce protocol was preceded by a 10-minute warm-up (i.e., treadmill walking at 1.0 mph, 0% grade). Conversely, Panza et al[16] and Garber et al[17] showed a significantly higher ischemic threshold for tests using the standard Bruce protocol than that for protocols with much lower work-rate increments. A possible explanation for the differences between these findings and ours is that the warm-up periods differed in duration among all low-level protocols that were compared against the standard Bruce protocol.

Starling et al[18] found a greater frequency of ischemic responses using the Bruce than the modified Naughton protocol, and noted higher peak heart rates and rate-pressure products during the former. Therefore, subjects may not have reached the ischemic threshold during the tests using the modified Naughton protocol. The same possible explanation for the 3 discordantly positive tests observed in the present study may also be true. In each of these patients, the peak heart rate using the modified Bruce protocol was lower than the heart rate at the onset of ischemic electrocardiographic changes using the standard Bruce test (110 vs 120, 94 vs 115 and 148 vs 150 beats/min, respectively).

Although the anginal threshold was also evaluated in this study, this end point was considered to be less conclusive, because of the subjective interpretation of establishing its exact time of onset. Although there were significant differences in mean heart rate and VO_2 at angina between protocols, rate-pressure product at onset of angina was similar between protocols.

Exercise responses at peak and submaximal exercise: Numerous investigators showed that rate-pressure product and heart rate alone have a good correlation with myocardial VO_2,[19–22] whereas others showed that the peak values of heart rate and rate-pressure product were highly reproducible during serial exercise testing on identical protocols.[1–12] The findings of this study demonstrated that mean heart rate, rate-pressure product and VO_2 were significantly greater at peak exercise during the standard than during the modified Bruce protocol, although the mean differences in peak variables between protocols were small. The fact that patients were able to achieve higher maximal values during the standard Bruce protocol is most likely due to peripheral muscle fatigue that developed during the modified Bruce tests in those patients (56%) who stopped because of fatigue on both tests, because mean exercise duration was approximately 5 minutes longer using this protocol. This longer time period on the

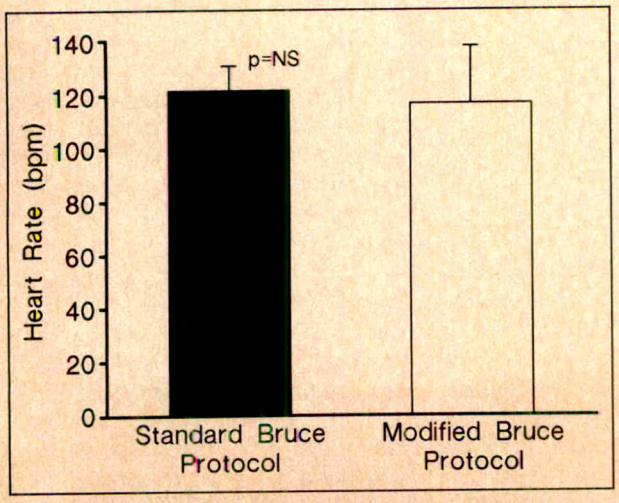


FIGURE 3. Heart rate at onset of ischemic ST-segment depression for concordantly positive tests. NS = not significant.

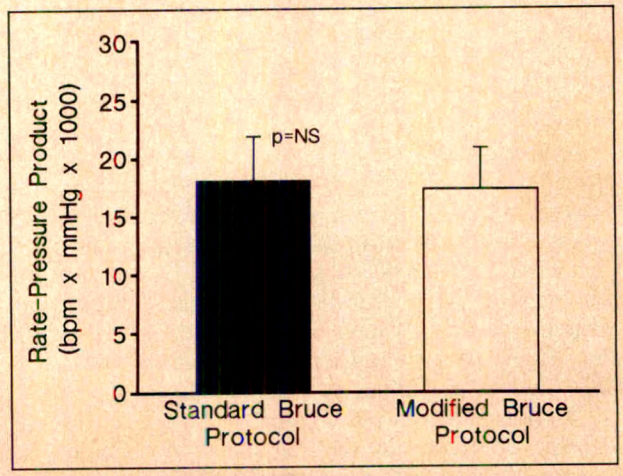


FIGURE 4. Rate-pressure product at onset of ischemic ST-segment depression for concordantly positive tests. NS = not significant.

treadmill (notably, while wearing the uncomfortable headgear and mouthpiece apparatus) may have also caused patients to be less motivated to continue exercising. Thus, the subjects were able to exercise to a higher exercise stage or longer into a given stage, or both, using the standard Bruce protocol.

The observed similarity of VO_2 at matched exercise levels between protocols is consistent with the physiologic principle that an absolute amount of exercise needs a set quantity of VO_2 for a subject to perform that level of exercise (given standardized conditions between tests). This study also demonstrates that other submaximal physiological responses to the standard and modified Bruce protocols are similar.

Study limitations: The findings of this study are limited to a comparison of exercise tests using the standard and modified Bruce protocols. It is possible that a longer warm-up period than occurs during the modified Bruce protocol, or a more abrupt protocol than the standard Bruce, or both, may affect these cardiopulmonary and ischemic variables. The use of diastolic blood pressure to monitor for any possible differences in vasodilation during tests using the 2 protocols was limited to obtaining a clear auscultatory distinction of diastolic blood pressures during exercise. To reduce the variability between measurements, blood pressures were obtained using the same methodology by the same observer for each exercise test.

In conclusion, these data indicate that exercise ischemic data obtained from patients who performed serial exercise tests using both the standard and the modified Bruce protocols can be equivalently compared, because there was no significant difference in the ischemic threshold between these protocols. These 2 frequently used protocols can also be used equivalently to elicit ischemic responses, because there was no significant difference in the frequency of exercise-induced ischemia between paired tests. Finally, physiologic variables such as heart rate, rate-pressure product and VO_2 at matched exercise stages were similar despite the difference in work-rate increments between protocols.

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Comparison Between Technetium-99m–Teboroxime and Thallium-201 Dipyridamole Planar Myocardial Perfusion Imaging in Detection of Coronary Artery Disease

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Technetium-99m (TC-99m)–teboroxime is a new myocardial perfusion imaging agent. The purpose of this prospective study was to compare Tc-99m–teboroxime with thallium-201 imaging after the administration of dipyridamole. Thirty patients referred for the evaluation of chest pain were studied with both thallium-201 and Tc-99m–teboroxime dipyridamole scans (mean interval 2 days). Dipyridamole was administered at 0.142 mg/kg/min for 4 minutes. Planar imaging (3 standard views) was obtained at 5 and 240 minutes after the injection of 2.2 mCi of thallium-201. Tc-99m–teboroxime (18 to 25 mCi) was injected after dipyridamole infusion. A second injection, at rest, was repeated 4 hours later. Planar imaging (3 standard views of 1 minute/view for the first 2 views, and 90 seconds for the last view) was obtained 2 minutes after Tc-99m–teboroxime injection. Blinded reading was performed by 3 observers. Thallium-201 showed perfusion defects in 182 myocardial segments corresponding to 33 of 45 (73%) significantly stenosed coronary arteries (≥70% reduction in endoluminal diameter), and Tc-99m–teboroxime detected 160 abnormal segments corresponding to 29 of 45 (64%) stenosed arteries. Thallium-201 and Tc-99m–teboroxime studies were normal in 3 patients. In conclusion, this study shows that there is a good correlation in the imaging results found with thallium-201 and Tc-99m–teboroxime using dipyridamole infusion on both a segmental and a diagnostic comparison.

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Technetium-99m (Tc-99m)–teboroxime (Tc-99m–SQ30217; Cardiotec™), a boronic acid adduct of technetium dioxime (BATO) compound, is a neutral lipophilic agent that rapidly diffuses across phospholipid membranes.[1–2] As a new Tc-99m–labelled myocardial perfusion imaging agent, it offers advantages over thallium-201. Tc-99m–teboroxime myocardial uptake is rapid, with excellent heart visualization at 2 minutes after injection.[3–5] Myocardial extraction of this new imaging agent exceeds that of either thallium-201 or Tc-99m–sestamibi.[6–8] This radiopharmaceutical also demonstrates a low lung uptake and rapid blood clearance. Myocardial clearance of Tc-99m–teboroxime is fast following a biexponential decrease.[9] Myocardial clearance is approximately 70% during the first 5 minutes after injection, and allows patients to perform stress and rest studies within 2 hours, and thus to obtain a rapid diagnosis.

Most studies of this agent were obtained with the injection performed at peak stress (usually on a treadmill).[10–12] However, because of the biological characteristics of Tc-99m–teboroxime, pharmacological coronary vasodilation is theoretically better suited than treadmill stress test for Tc-99m–teboroxime imaging. This prospective study compares thallium-201 and Tc-99m–teboroxime dipyridamole planar imaging in the detection of coronary artery disease on both a segmental and a diagnostic comparison.

METHODS

Study patients: 30 patients referred for the evaluation of chest pain or for coronary angiography were enrolled in this prospective study. For each patient, Tc-99m–teboroxime and thallium-201 scans were performed using dipyridamole as a pharmacological "stress test" with a mean interval of 2 days between the 2 studies. Twenty-five of these patients underwent coronary angiography. Written informed consent was obtained from each patient and the protocol used was approved by the ethics committee of our institution. Patients with severe congestive heart failure, previous cardiac surgery or intervention, and significant valvular heart disease or severe pulmonary disease, women of child-bearing age, and patients with known allergy to dipyridamole or aminophylline were excluded from this study.

Dipyridamole infusion: The same preparation was used for each test. Patients fasted for 8 to 12 hours before dipyridamole administration. Drugs and foods containing methylxanthines were discontinued ≥24 hours

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before the test. An intravenous catheter was inserted in an antecubital vein. Dipyridamole was administered intravenously at a rate of 0.142 mg/kg/min over 4 minutes. Patients were then instructed to walk in place for 2 minutes. The radiopharmaceutical (thallium-201 or Tc-99m–teboroxime) was injected as a bolus. The patient continued to walk in place for 1 additional minute. Vital signs were monitored before, during and for 15 minutes after dipyridamole administration. Aminophylline was used only in cases of severe side effects or symptoms related to dipyridamole infusion.

Thallium-201 study: A bolus of thallium-201 (2.5 mCi) was injected intravenously after 2 minutes of low-level exercise after administration of dipyridamole. Planar myocardial imaging began approximately 5 minutes later, using 3 standard views (45° left anterior oblique and anterior supine views, and left lateral view, with the patient being placed in right decubitus). Redistribution images were obtained 3 to 4 hours later (average 235 ± 15 minutes). Images were acquired on a small field-of-view gamma camera equipped with a low-energy, all-purpose, parallel hole collimator and interfaced to a Medical Data System computer. The acquisition time was 7 min/view on a 128 × 128 matrix.

Technetium-99m–teboroxime study: TECHNETIUM-99M-TEBOROXIME LABELLING: Tc-99m–teboroxime was available in a lyophilized form disposed in a vial. One hundred mCi of Tc-99m–pertechnetate in 1 ml of 0.9% sodium chloride solution was added to the vial for reconstitution. Then the vial was placed in a boiling water bath (100°C) for 15 minutes in a stationary, upright position. Thin layer chromatography was performed to determine the percentage of free Tc-99m–pertechnetate and reduced hydrolyzed Tc-99m. Tc-99m–teboroxime was injected when the sum of the 2 previous percentages did not exceed 10% (labelling efficiency >90%).

TECHNETIUM-99M-TEBOROXIME IMAGING: A same-day stress-rest injection protocol was used for Tc-99m–teboroxime imaging. After dipyridamole infusion, the same type of low-level exercise as for thallium-201 imaging was performed for 2 minutes, followed by the injection of 18 to 25 mCi of Tc-99m–teboroxime. The exercise was continued for 1 minute after the radiopharmaceutical injection. Planar imaging began at approximately 90 to 120 seconds after the intravenous injection of Tc-99m–teboroxime using the same gamma camera and collimator as for thallium-201 imaging. The first 2 planar images (supine anterior and 45° left anterior oblique views) were obtained at 60 seconds/view, and the last view (left lateral, patient sitting with his left side close to the camera) lasted 90 seconds. In two cases, the patient was lying down during the acquisition of the lateral view because of his clinical condition. Approximately 4 hours later (average 240 ± 75 min), a second injection of 20 of 25 mCi of Tc-99m–teboroxime was performed at rest. Two minutes later, planar imaging was repeated in the same 3 standard views, with the same acquisition parameters used for the stress study.

Data analysis: All myocardial studies were analyzed qualitatively and quantitatively. Each study was interpreted by 3 independent observers unaware of the patient's history, pharmacological "stress" test result or coronary anatomy. The reading of thallium-201 and Tc-99m–teboroxime studies was performed independently. Disagreements between the different observers were resolved by consensus. Interpretation of thallium-201 scans was primarily based on analog images and semi-quantitative analysis with segmental activity profiles of opposing myocardial walls using digital images after a 10% uniform background subtraction. This display was used for both initial and redistribution studies. The Tc-99m–teboroxime images were also available in 2 presentations (an analog image and a digital black and white display with a uniform background subtraction of 10%). The left ventricle was arbitrarily divided into 5 segments in each view for segmental comparison between Tc-99m–teboroxime and thallium-201. Each segment was characterized as being normal, ischemic or scar. For each study, 15 segments (5 segments/view) per patient were evaluated for a total of 450 segments for the 30 patients. The observers were asked to determine the final diagnosis for each patient according to thallium-201 and Tc-99m–teboroxime scan results, allowing a diagnostic comparison between these 2 modalities. Each final diagnosis was characterized as being normal, ischemic or scar. The results of thallium-201 and Tc-99m–teboroxime studies were correlated with those of coronary angiography. For this purpose, the perfusion defects identified on myocardial scans were related to a specific major coronary territory (left anterior descending, circumflex and right coronary arteries).[13] Semi-quantitative analysis was used to assess the relative severity of ischemia. Ischemic/normal wall ratios were determined for both thallium-201 and Tc-99m–teboroxime studies. Three regions of interest were chosen for each patient with ischemic defects (either on thallium-201 or Tc-99m–teboroxime studies) on the same views for both dipyridamole and rest imaging. The regions had the same location and size for thallium-201 and Tc-99m–teboroxime in a given patient. The 3 regions of interest were placed over a normally perfused myocardial wall, an ischemic wall and the left lung. The latter region was used as a background value for subtraction. For each region, count density was measured, and the results were expressed as the average number of counts per pixel.

Coronary angiography: Twenty-five patients underwent coronary angiography and left ventriculography using the Judkins technique with multiple views of the right and left coronary arteries. This test was performed within 3 months of the thallium-201 study. Coronary angiograms were interpreted by 2 independent observers. Differences in interpretation were resolved by consensus. Significant coronary artery stenosis was defined as a ≥70% reduction in endoluminal diameter of ≥1 major coronary artery.

Statistical analysis: All results are expressed as mean ± 1 standard deviation. Concordance tables were used for comparison between thallium-201 and Tc-99m–teboroxime scintigraphic images on both a segmental and a diagnostic basis. Coronary angiography was considered as the reference test. The sensitivity of both scintigraphic studies in detection of coronary

artery disease was defined as the number of abnormally perfused coronary territories found on scintigraphic studies in comparison with those detected by coronary angiography and was expressed as: true positive tests/sum of true positive plus false negative tests × 100. Serial changes in heart rate and systolic blood pressure were analyzed by Student's *t* test for paired measures. McNemar test for related proportions was used to compare the diagnostic sensitivity of Tc-99m–teboroxime to that of thallium-201. Convergence of Tc-99m–teboroxime with thallium-201 was evaluated using a kappa (Cohen) analysis.

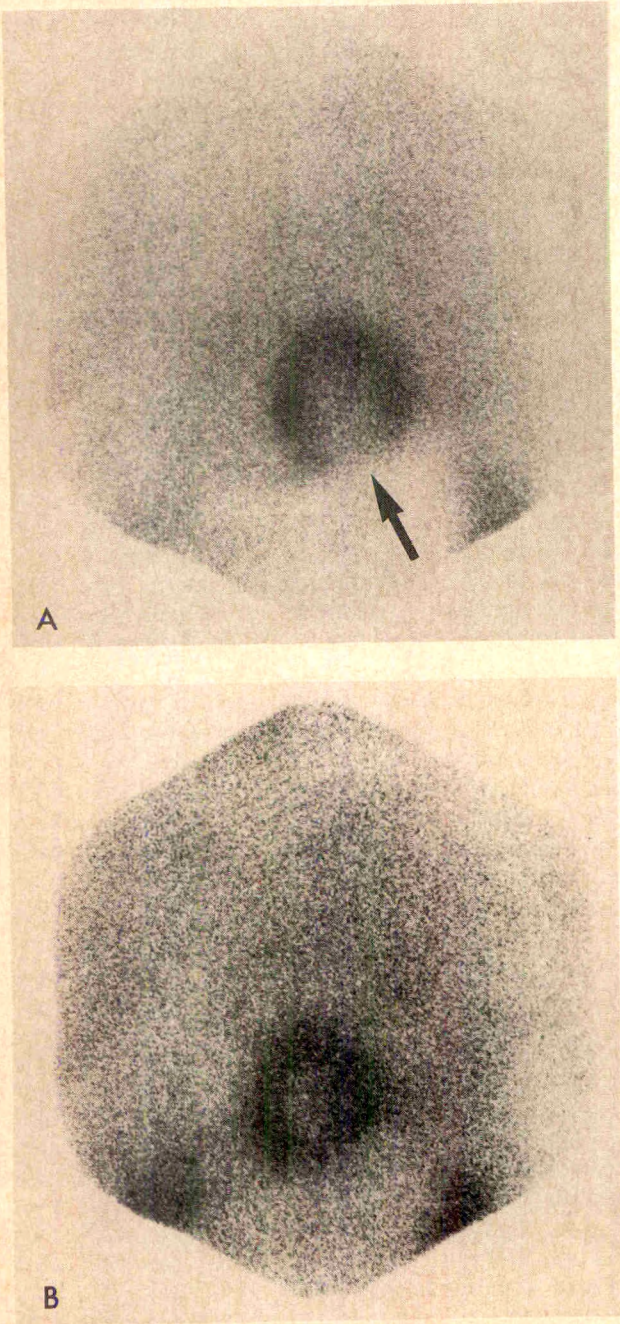


FIGURE 1. Technetium-99m–teboroxime study (45° left anterior oblique view) obtained 2 minutes after injection of 20 mCi, after dipyridamole infusion *(A)*, and 2 minutes after injection at rest *(B)* in patient with 95% stenosis of right coronary artery. Perfusion defect *(arrow)* detected on dipyridamole study is not seen on study at rest (ischemic defect).

RESULTS

Study patients: The group of patients consisted of 9 women and 21 men, aged 35 to 83 years (mean age 63 ± 10). Four patients had a previous myocardial infarction. Except for 1 patient, all thallium-201 studies were performed before Tc-99m–teboroxime imaging, with a mean interval of 2.0 ± 0.8 days. Coronary angiography was performed before the thallium-201 and Tc-99m–teboroxime studies in 17 of the 25 patients who had coronary angiography within 3 months. Eleven patients had 1-vessel, 8 had 2-vessel, and 6 had 3-vessel disease. No patient had a left main coronary artery disease.

The changes in hemodynamic parameters related to intravenous dipyridamole infusion were similar for both thallium-201 and Tc-99m–teboroxime studies (p = not significant). Decreases in systolic blood pressure were 12 ± 4 and 11 ± 6 mm Hg for thallium-201 and Tc-99m–teboroxime, respectively, and increases in heart rate were 8 ± 6 and 9 ± 6 beats/min for thallium-201 and Tc-99m–teboroxime, respectively. No serious adverse reaction such as myocardial infarction or severe respiratory distress occurred during or after dipyridamole administration. Intravenous aminophylline was administered for side-effect relief in 10 and 8 patients during thallium-201 and Tc-99m–teboroxime dipyridamole studies, respectively.

Segmental comparison between thallium-201 and technetium-99m–teboroxime studies: An overall agreement was found in 382 of the total 450 (85%) myocardial segments studied when thallium-201 and Tc-99m–teboroxime scans (Figures 1 to 3) were compared on a segmental basis (k = 0.70). Table I summarizes the results of the segmental analysis. Fifty-five percent of all segments were classified as being normal on both scintigraphic studies. The total number of ischemic segments detected by each myocardial perfusion study was similar (164 [36%] for thallium-201, and 142 [32%] for Tc-99m–teboroxime). Thirty-six segments (8%) were found to be ischemic with thallium-201, but normal with Tc-99m–teboroxime, whereas 20 (5%) were normal with thallium-201, but ischemic with Tc-99m–teboroxime. The ischemic/normal wall ratios after dipyridamole were 0.73 ± 0.10 for thallium-201 (0.95 ± 0.07 on delayed imaging), and 0.70 ± 0.11 for Tc-99m–teboroxime (0.97 ± 0.08 at rest).

Comparison between thallium-201 and technetium-99m–teboroxime; patient's final diagnosis: The patient's final diagnosis, performed by the observers, was concordant for both scintigraphic studies in 28 of 30 (93%) patients ($\kappa = 0.77$). Thallium-201 and Tc-99m–teboroxime were both normal in 2 patients, showed ischemic defects in 24, and scars in 2 (Table II). Disagreement was seen in 2 patients. In the first patient, with significant stenosis of the circumflex and right coronary arteries on coronary angiography, a transient perfusion defect was seen on thallium-201 scan, whereas the Tc-99m–teboroxime study was interpreted as normal. In the second patient, with proven stenosis of the

circumflex artery, the Tc-99m–teboroxime study detected a transient perfusion defect of the lateral wall of the left ventricle that was not seen on the thallium-201 study.

Correlation with coronary angiography: Coronary angiography performed in 25 patients showed significant stenosis in 45 major coronary arteries. The left anterior descending artery was significantly stenosed in 13 patients, the circumflex in 15, and the right coronary artery in 17. Myocardial perfusion defects were seen in 182 segments on thallium-201 study, detecting 33 of 45 (73%) stenosed coronary arteries. Tc-99m–teboroxime detected 160 segments with perfusion defects, corresponding to 29 of 45 (64%) stenosed arteries. Table III summarizes the sensitivity of both studies in detection of territories supplied by stenotic coronary arteries (p = not significant).

DISCUSSION

Tc-99m–teboroxime is a neutral, lipophilic agent that has recently been introduced for clinical myocardial perfusion imaging. Besides its labelling to Tc-99m, Tc-99m–teboroxime has 2 unique characteristics: a high extraction fraction with linear uptake over a wide range

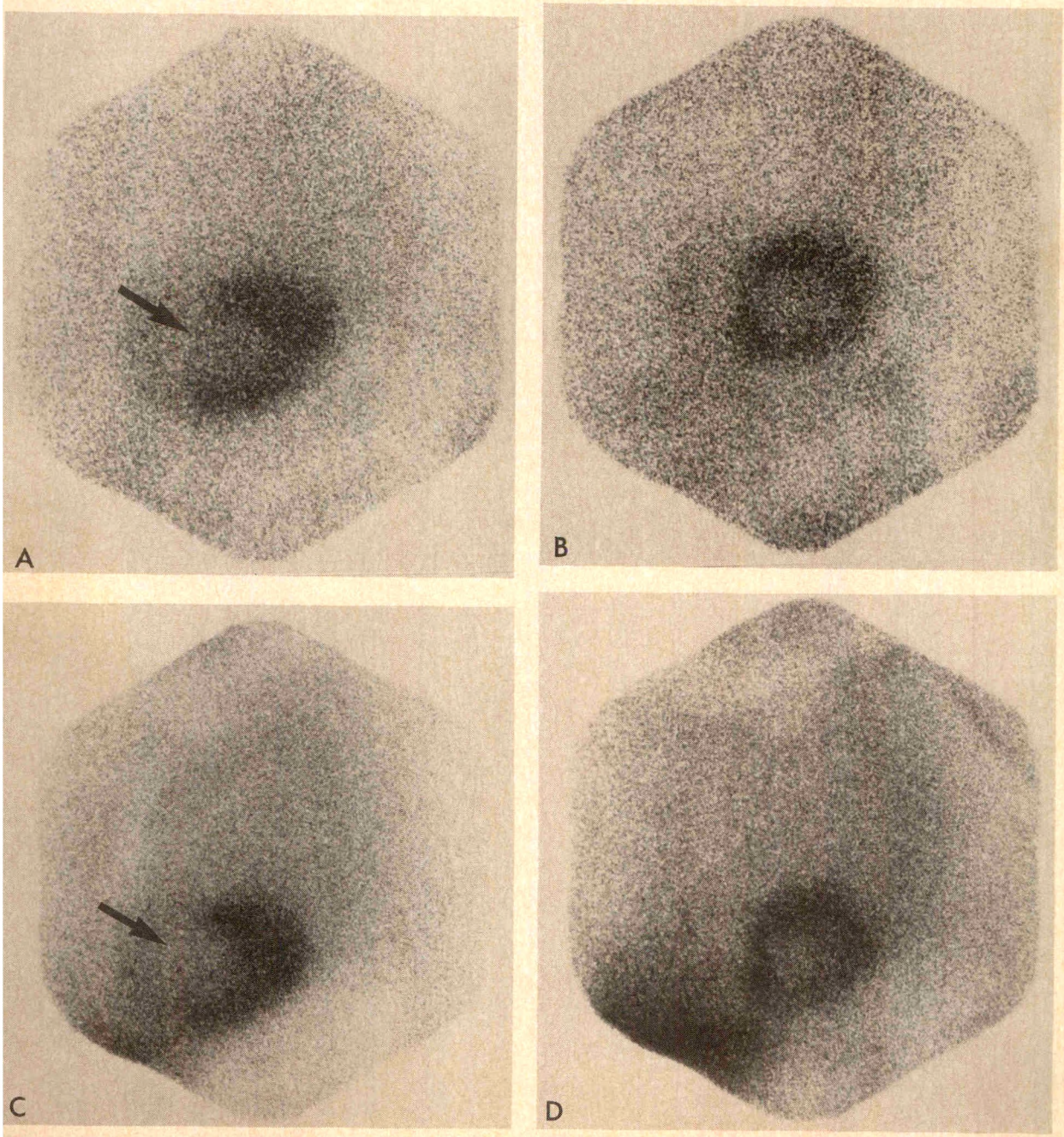


FIGURE 2. Thallium-201 (*A*, dipyridamole; *B*, delayed imaging) and technetium-99m–teboroxime (*C*, dipyridamole; *D*, at rest) studies in patient with 90% stenosis of left anterior descending artery. Both studies (45° left anterior oblique view) show ischemic defect involving septal wall (*arrows*).

of myocardial blood flows, and a very rapid myocardial clearance that is biexponential, with effective half-lives of 5 minutes (66% of injected dose) and 3.8 hours (33% of injected dose).[3] Thus, myocardial imaging must be completed very rapidly after the Tc-99m–teboroxime injection. Most of the studies using this new radiopharmaceutical were performed with the injection of Tc-99m–teboroxime during a treadmill stress test.

Tc-99m–teboroxime dipyridamole imaging (or with other pharmacological intervention) may represent a more convenient way to use this agent in clinical practice, because imaging can begin without significant delay. Contrary to the Tc-99m–teboroxime treadmill stress test where the treadmill ideally should be adjacent to the gamma camera, the Tc-99m–teboroxime dipyridamole protocol can be performed close to the imaging device without specific technical set-up. Since myocardial imaging must be performed rapidly after the injection, some artifacts related to the increased respiratory movements and upward creep motion of the heart after a maximal stress test may be introduced. This can lead to image degradation. There is usually no such increased movement immediately after administration of dipyridamole. Another advantage to the use of

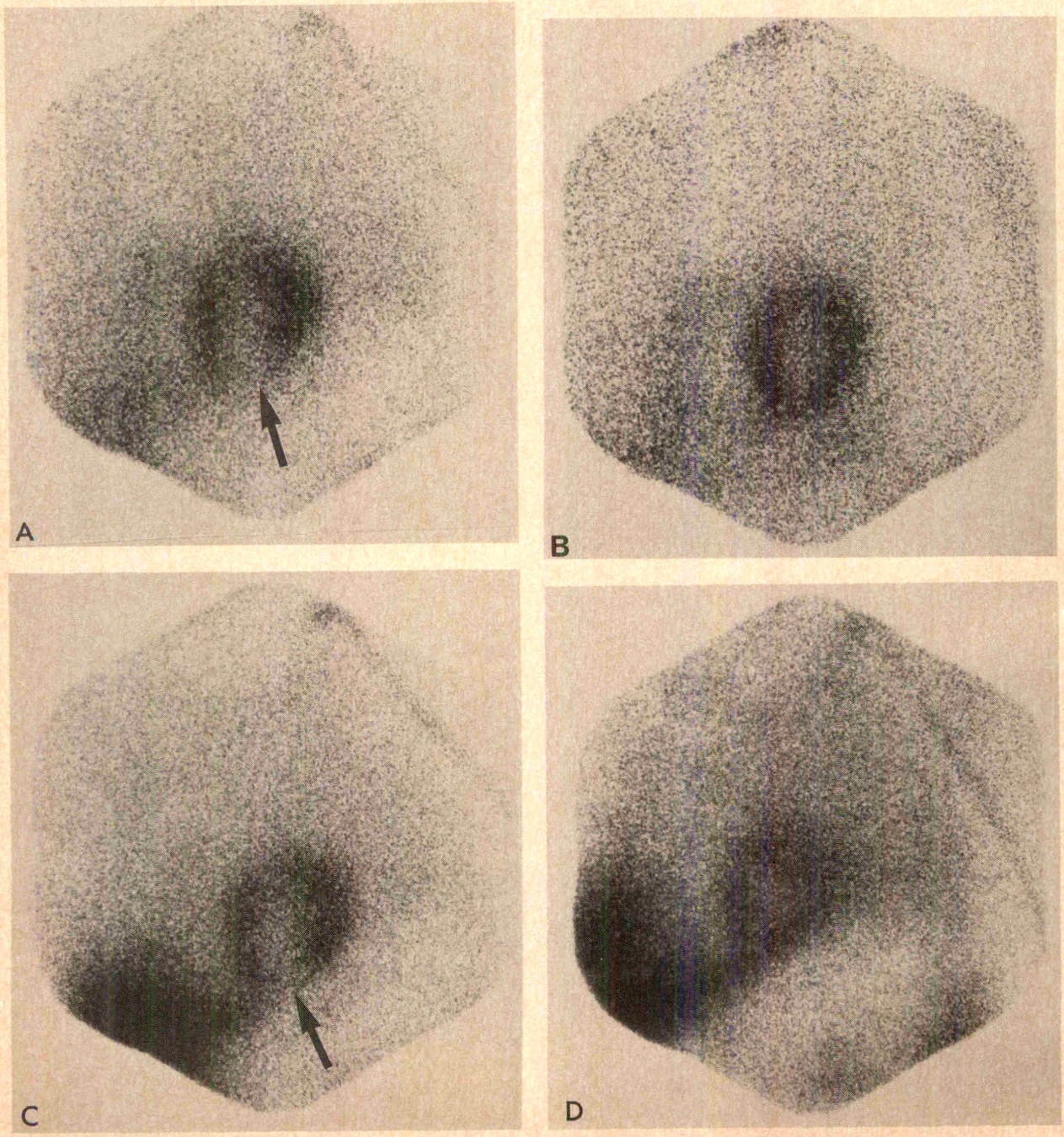


FIGURE 3. Thallium-201 (*A*, dipyridamole; *B*, delayed imaging) and technetium-99m–teboroxime (*C*, dipyridamole; *D*, at rest) studies in patient with 95% stenosis of right coronary artery, and 75% stenosis of left anterior descending artery. There is severe transient perfusion defect of inferior wall *(arrows)* and slight ischemia of septal wall on both studies.

TABLE I Comparison Between Thallium-201 and Technetium-99m-Teboroxime Studies: Segmental Analysis

	Technetium-99m-Teboroxime		
Thallium-201	Normal (%)	Ischemia (%)	Scar (%)
Normal	248 (55)	20 (4.5)	—
Ischemia	36 (8)	122 (27)	6 (1)
Scar	6 (1)	—	12 (3)

Agreement: 85% (382 of 450)

TABLE II Comparison Between Thallium-201 and Technetium-99m-Teboroxime Studies: Patient Diagnosis Analysis

	Technetium-99m-Teboroxime		
Thallium-201	Normal	Ischemia	Scar
Normal	2	1	—
Ischemia	1	24	—
Scar	—	—	2

Agreement: 93% (28 of 30)

TABLE III Comparison Between Thallium-201 and Technetium-99m-Teboroxime Studies: Correlation with Coronary Angiography in Detection of Significant Stenosis

Coronary Artery	Thallium-201 (%)	Technetium-99m-Teboroxime (%)
Left anterior descending	10 of 13 (77)	9 of 13 (69)
Left circumflex	11 of 15 (73)	10 of 15 (67)
Right	12 of 17 (71)	10 of 17 (68)
Total	33 of 45 (73)	29 of 45 (64)

dipyridamole (maximal coronary hyperemia) as a stress test for Tc-99m–teboroxime imaging is the linear Tc-99m–teboroxime myocardial uptake at high flow rates and myocardial extraction fraction, contrary to Tc-99m–sestamibi and thallium-201-thallous chloride.[8] This may theoretically result in a decrease of the ischemic/normal wall ratio and in subsequent improvement in the detection of coronary artery disease. However, the fast myocardial washout of Tc-99m–teboroxime after its rapid initial uptake may decrease this effect. This hypothesis needs to be tested in a human study comparing Tc-99m–teboroxime dipyridamole to Tc-99m–teboroxime treadmill stress test imaging.

The main purpose of this study was to compare Tc-99m–teboroxime with thallium-201 planar imaging after dipyridamole administration. A good correlation in the imaging results was found with these 2 radiopharmaceuticals on both a segmental (85%) and a patient diagnosis (93%) basis. Twenty-eight patients had the same final diagnosis on both thallium-201 and Tc-99m–teboroxime imaging. These results are similar to those obtained in a previous study comparing Tc-99m–teboroxime and thallium-201 planar imaging, but using a treadmill as the stress modality.[10] A similar correlation was found between Tc-99m–sestamibi and thallium-201 planar myocardial imaging with a segmental and diagnostic agreement of 89% in detection of coronary artery disease.[14] Using coronary angiography as the gold standard, the sensitivity of Tc-99m–teboroxime in detection of myocardial territories supplied by significantly stenosed coronary arteries was 64%, whereas that of thallium-201 was 73%. There was no significant statistical difference between thallium-201 and Tc-99m–teboroxime in detection of any of the 3 major coronary arteries.

Study limitations: The study cohort was highly selected, with 83% of the subjects undergoing coronary angiography either before or after Tc-99m–teboroxime and thallium-201 imaging. Furthermore, all coronary angiographies were abnormal, indicating that this cohort had a large percentage of patients with coronary artery disease. Thus, the statistics do not reflect the sensitivity of these tests performed in the general population. No data on the specificity were obtained in this study. Because the clinical imaging experience with Tc-99m–teboroxime is quite limited, there are many technical issues that need to be addressed. In the present study, a rapid data acquisition protocol was used for imaging because of the rapid myocardial clearance and the possibility of early myocardial redistribution. Previous studies with prolonged acquisition time >5 minutes after injection of Tc-99m–teboroxime reported a lower diagnostic accuracy[9] than did a more recent study using a short acquisition protocol.[10] Although myocardial perfusion imaging with single photon emission computerized tomography is now widely available, planar acquisition was chosen because of the limitations related to Tc-99m–teboroxime single photon emission computerized tomography imaging, mainly with a single detector gamma camera.[15] Although no significant difference was observed in this study in the ability of thallium-201 or Tc-99m–teboroxime to identify areas of ischemic myocardium based on whether aminophylline was used it is possible that the washout of Tc-99m–teboroxime was accelerated during hyperemia, which was not abated by the use of aminophylline.

The image acquisition protocol used in this study began with the best septal view, followed by the anterior and left lateral view. Because of the prominent liver uptake and "shine-through" of the liver activity, the inferior wall was "masked" on the left lateral view in many patients. It may be useful to begin the imaging with the left lateral view first, followed by the best septal and anterior views, because on these latest views, the liver uptake does not usually represent a significant imaging limitation. It can be particularly useful after dipyridamole infusion, because the splanchnic and liver uptake then is more important than after an injection at stress. Furthermore, imaging in the upright position may help to lower the liver, allowing a better delineation from the heart. More extensive clinical use of Tc-99m–teboroxime will help to define the optimal imaging protocol. Interpretation of Tc-99m–teboroxime studies was primarily based on the planar analog images and, if necessary, on a digital display with a uniform background subtraction. At the present time, the best method for quantitative assessment of Tc-99m–teboroxime planar imaging has not yet been established.

In conclusion, the data of this study showed that there is a good correlation in the imaging results found

with thallium-201 and Tc-99m–teboroxime planar myocardial perfusion imaging using dipyridamole as a pharmacological stress test on both a segmental and a diagnostic comparison.

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Exercise Testing and Thallium-201 Emission Computed Tomography in Patients with Intraventricular Conduction Disturbances

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The specificity of exercise thallium-201 emission computed tomography for coronary artery disease was assessed in patients with intraventricular conduction disturbances. Eighty-seven patients were studied: 33 with right bundle branch block (RBBB), 11 with RBBB and left-axis deviation, 11 with left (L)BBB, 12 on right ventricular pacing, and 20 with Wolff-Parkinson-White (WPW) syndrome. A control group of 349 consecutive patients with normal intraventricular conduction was also examined. The specificity of diagnosis of coronary artery disease in patients with LBBB (30%), right ventricular pacing (44%) or RBBB plus left-axis deviation (50%) was significantly lower than in patients with normal intraventricular conduction (94%; $p < 0.01$). In contrast, there was no significant difference between specificity in patients with RBBB (86%) or WPW syndrome (90%) and patients with normal intraventricular conduction. Perfusion defects were found in the anterior, septal and inferior segments in patients with LBBB, and in the septal and inferior segments in patients with RBBB plus left-axis deviation despite the absence of coronary stenosis. Furthermore, diffuse slow washout was seen more often in patients with WPW syndrome (35%) than in controls who had normal intraventricular conduction (11%; $p < 0.05$), despite a good exercise performance in the former group. This study suggests that there is an increased incidence of abnormal perfusion and clearance during exercise thallium-201 emission computed tomography in patients with intraventricular conduction disturbances.

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Results from several centers have shown that exercise thallium-201 myocardial imaging is more sensitive and specific for detecting myocardial ischemia than conventional exercise electrocardiography.[1–6] Thallium-201 myocardial scintigraphy has been especially recommended for noninvasive evaluation of coronary artery disease in patients with intraventricular conduction disturbances, since the electrocardiographic diagnosis of coronary artery disease is difficult in such patients.[1,7] However, perfusion defects in patients with left bundle branch block (LBBB) or ventricular preexcitation have been described in exercise myocardial imaging despite the absence of angiographic coronary stenosis.[8–11]

The present study was performed to determine the specificity of exercise thallium-201 emission computed tomography for detecting epicardial coronary stenosis in patients with various types of intraventricular conduction disturbances, and to assess the value of exercise thallium-201 emission computed tomography for the diagnosis of coronary artery disease in such patients.

METHODS

Patients: The study group consisted of 97 consecutive patients with various types of intraventricular conduction disturbances who underwent exercise thallium-201 myocardial imaging to investigate the presence of coronary artery disease as a cause of intraventricular conduction disturbance, chest pain or ST depression on exercise electrocardiography. Ten patients were excluded owing to apparent underlying heart disease after a careful assessment of the history, clinical findings, chest x-ray (cardiothoracic ratio >55%) and echocardiogram (wall thickness >15 mm, left ventricular ejection fraction <50%). The remaining 87 patients (67 men and 20 women, mean age 59 ± 14 years) were studied. They had the following conditions: RBBB, 33 (mean age 61 ± 12 years); RBBB plus abnormal left-axis deviation, 11 (mean age 63 ± 8 years); LBBB, 11 (mean age 66 ± 8 years); right ventricular pacing, 12 (mean age 67 ± 7 years); and Wolff-Parkinson-White (WPW) syndrome, 20 (mean age 35 ± 16 years). Abnormal left-axis deviation was defined as leftward deviation of the mean QRS axis in the frontal plane to ≥−30°. The 12 patients with right ventricular pacing had received implantation of DDD mode or VVI mode pacemakers (DDD, 7; VVI or VVIR, 5) because of complete atrioventricular block. All the patients with RBBB plus left-axis deviation, LBBB and right ventricular pacing underwent coronary angiography. Because the 20 patients with

TABLE I Results of Thalluim-201 Emission Computed Tomography in Patients with Right Bundle Branch Block and Left-Axis Deviation

Pt.	Age (yr) & Sex	DP	Thallium-201 ECT									Abnormal Washout Rate Location	Coronary Angiography % Diameter Stenosis		
			ANT		SEP		INF		LAT		AP				
			A1	A2	S1	S2	I1	I2	L1	L2			LAD	LC	Right
1	64 M	25,740	N	N	T	N	T	T	N	N	N	S I L	0	0	0
2	60 F	18,040	N	N	N	N	N	N	N	N	N	DSW	0	0	0
3	73 M	27,872	N	N	T	N	P	T	N	N	N	S I	0	0	0
4	69 M	37,200	N	N	T	N	T	T	N	N	N	S I	0	0	0
5	73 M	25,650	N	N	N	N	T	T	N	N	N	I	0	0	0
6	65 M	20,296	P	N	T	N	T	T	N	N	N	S I	0	0	0
7	70 M	29,880	N	N	N	N	N	N	N	N	N	S I	0	0	0
8	59 M	19,024	N	N	N	N	N	N	N	N	N	—	0	0	0
9	64 M	34,104	N	N	N	N	N	N	N	N	N	—	0	0	0
10	46 M	35,280	N	N	N	N	N	N	N	N	N	—	0	0	0
11	55 M	21,216	P	P	P	P	N	N	N	N	P	—	90	0	0

ANT, A = anterior; AP = apical; BBB = bundle branch block; DP = double product; DSW = diffuse slow washout; ECT = emission computed tomography; INF, I = inferior; LAD = left anterior descending; LAT, L = lateral; LC = left circumflex; N = normal; P = persistent defect; SEP, S = septal; T = transient defect.

WPW syndrome had neither signs nor symptoms of coronary artery disease, only 1 underwent coronary angiography.

Three hundred forty-nine consecutive patients who had normal intraventricular conduction and no heart disease other than possible coronary artery disease underwent exercise thallium-201 emission computed tomography and coronary angiography for chest pain or ventricular arrhythmia, or both. Seventy-four of them were diagnosed as having no coronary artery disease after coronary angiography.

Coronary angiography: Coronary angiography was performed within 3 months of exercise thallium myocardial imaging and was assessed by visual interpretation. Significant coronary stenosis was defined as a >50% luminal narrowing of 1 or more of the main coronary arteries.

Thallium image acquisition and analysis: The exercise thallium imaging methods have been described.[12] In brief, all patients underwent symptom-limited maximal exercise testing on an upright bicycle ergometer. At peak exercise, 3.5 mCi of thallium-201 was injected intravenously and the patient was encouraged to continue exercising for an additional 30 to 60 seconds. Myocardial images were obtained with a rotating gamma camera (ZLC 7500, Siemens) equipped with a high-resolution parallel-hole collimator and interfaced with a computer system (Scintipac 2400, Shimadzu). Thirty-two planar acquisitions were performed for 20 seconds over 180°. Initial imaging was begun within 10 minutes after the completion of exercise and delayed images were obtained 4 hours after injection. Orthogonal images were generated by oblique angle reconstruction to produce 6 mm thick vertical long-axis, short-axis and horizontal long-axis slices. In both the initial and delayed images, the uptake of thallium-201 was determined visually for each of the 9 segments (Figure 1) using a 4 point scoring system (3 = normal, 2 = mildly reduced, 1 = moderately reduced, and 0 = markedly reduced). The computer method of quantifying washout rate has been described previously.[12] Normal limits for the washout rate were established in 15 normal subjects. An abnormal washout rate was defined as being >2 standard deviations below the mean normal value.

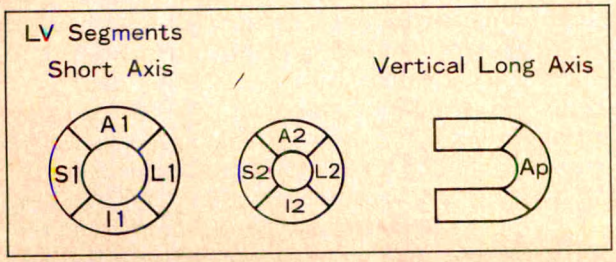


FIGURE 1. Nine regions of interest on 2 reconstructed short-axis and 1 vertical long-axis slice. A1, S1, I1 and L1 = basal anterior, septal, inferior and lateral segments; A2, S2, I2 and L2 = apical anterior, septal, inferior and lateral segments; Ap = apical segment; LV = left ventricular.

When the uptake score of a segment in the initial image was 0 or 1 and the score for the delayed image increased with abnormal washout rate, we defined the segment as showing a transient defect. A persistent defect was defined when the uptake score of a segment in the initial image was 0 or 1 and the score did not change in the delayed image. When washout was diffusely abnormal in all 9 segments, we defined such patients as having a diffuse slow washout.

Statistical methods: Data were expressed as either mean ± 1 standard deviation or percentages. Percent differences between 2 groups were compared by the chi-squared test. Comparisons among groups of patients were performed by 1-way analysis of variance. Differences were considered significant at a p value <0.05 (2-sided).

RESULTS

Results of exercise testing: Patients with normal intraventricular conduction exercised on a bicycle ergometer to a peak heart rate of 134 ± 22 beats/min. Peak heart rates of the patients with RBBB, RBBB plus left-axis deviation, LBBB, right ventricular pacing, and WPW syndrome were 135 ± 30, 140 ± 21, 143 ± 22,

TABLE II Results of Thallium-201 Emission Computed Tomography in Patients with Left Bundle Branch Block

Pt.	Age (yr) & Sex	DP	Thallium-201 ECT									Abnormal Washout Rate Location	Coronary Angiography % Diameter Stenosis		
			ANT		SEP		INF		LAT						
			A1	A2	S1	S2	I1	I2	L1	L2	AP		LAD	LC	Right
1	73 F	22,680	T	T	T	N	N	N	N	N	N	A S AP	0	0	0
2	72 F	14,700	T	T	T	T	N	N	N	N	T	A S AP	0	0	0
3	61 F	26,416	T	T	T	T	N	N	N	N	N	A S	0	0	0
4	66 M	28,712	N	N	T	T	T	N	N	N	N	S I	0	0	0
5	62 F	26,690	N	N	N	N	N	N	N	N	N	—	0	0	0
6	49 F	30,644	N	T	N	N	N	N	N	N	N	A	0	0	0
7	69 F	30,176	N	N	N	N	N	N	N	N	N	S	0	0	0
8	77 M	17,710	N	N	N	N	N	N	N	N	N	—	0	0	0
9	69 F	13,000	N	N	N	N	P	T	N	N	T	I AP	90	100	90
10	73 M	32,184	N	N	T	T	T	T	N	N	P	DSW	0	0	0
11	60 M	31,020	N	N	T	T	N	N	N	N	P	S	0	0	0

Abbreviations as in Table I.

TABLE III Results of Thallium 201 Emission Computed Tomography Patients with Right Ventricular Pacing

Pt. (mode)	Age (yr) & Sex	Thallium-201 ECT									Abnormal Washout Rate Location	Coronary Angiography % Diameter Stenosis		
		ANT		SEP		INF		LAT						
		A1	A2	S1	S2	I1	I2	L1	L2	AP		LAD	LC	Right
1 (DDD)	62 M	N	N	T	T	T	T	N	N	T	A S I AP	0	0	0
2 (VVIR)	62 M	N	N	N	N	N	N	N	N	N	—	0	0	0
3 (VVI)	66 F	N	T	T	T	T	T	N	N	N	A S I	0	0	0
4 (VVI)	75 F	N	N	N	N	N	N	N	N	N	—	0	0	0
5 (DDD)	58 M	N	N	T	T	T	N	N	N	P	DSW	0	0	0
6 (DDD)	66 F	N	N	N	T	N	N	N	N	T	—	0	0	0
7 (DDD)	69 M	N	N	T	N	N	P	N	N	T	S I AP	0	0	0
8 (DDD)	65 F	N	N	N	N	N	N	N	N	N	—	0	0	0
9 (VVI)	62 M	N	N	N	N	N	N	N	N	N	—	0	0	0
10 (VVI)	68 M	T	T	T	T	P	P	N	N	T	A S AP	90	95	90
11 (VVI)	83 F	N	T	N	T	N	N	N	N	T	—	90	75	90
12 (DDD)	69 M	N	P	T	T	T	T	N	N	P	S I	90	95	90

Abbreviations as in Table I.

101 ± 28, and 159 ± 17, respectively. No patient without coronary artery disease stopped because of angina.

Incidence of transient or persistent defects, or both, in patients with coronary artery disease: Two hundred seventy-five of the 349 patients with normal intraventricular conduction who underwent coronary angiography had significant coronary narrowings. Of these 275 patients, 255 had perfusion defects. The sensitivity of diagnosis of epicardial coronary artery disease by thallium-201 myocardial imaging was 93%. In contrast, 11 of 33 patients with RBBB, 1 of the 11 patients with RBBB plus left-axis deviation, 1 of the 11 patients with LBBB and 3 of the 12 patients with right ventricular pacing tested had significant coronary artery disease on coronary angiography (Tables I to IV). All patients with intraventricular conduction disturbance and coronary artery disease had perfusion defects.

Incidence of transient defects in patients without coronary artery disease: PATIENTS WITH NORMAL INTRAVENTRICULAR CONDUCTION (CONTROL GROUP): Seventy-four patients had normal epicardial coronary arteries on coronary angiography. Because only 4 of the 74 had transient defects on exercise thallium-201 myocardial imaging (5.4%), the specificity for the diagnosis of epicardial coronary artery disease was 94%.

GROUP WITH RIGHT BUNDLE BRANCH BLOCK: Three of 22 patients had transient defects. The specificity, 86%, was not significantly different from that in the control group (p = not significant).

GROUP WITH RIGHT BUNDLE BRANCH BLOCK PLUS LEFT-AXIS DEVIATION (TABLE I): Five of 10 patients who had no significant angiographic coronary artery stenosis had transient defects. The specificity (50%) was significantly lower than that seen in the control group ($p < 0.01$). An example from this group is shown in Figure 2.

GROUP WITH LEFT BUNDLE BRANCH BLOCK (TABLE II): Seven of 10 patients who had no significant angiographic coronary stenosis had transient defects and the specificity (30%) was significantly lower than that seen in the control group ($p < 0.01$). An example of this type of patient is shown in Figure 3.

GROUP WITH RIGHT VENTRICULAR PACING (TABLE III): Five of 9 patients who had no significant angiographic coronary narrowing had transient defects, and the specificity (44%) was significantly lower than that noted in the control group ($p < 0.01$).

TABLE IV Results of Thallium-201 Emission Computed Tomography in Patients with Wolff-Parkinson-White Syndrome

Pt.	Age (yr) & Sex	Location of Bypass Tract	Double Product	Thallium-201 ECT									Abnormal Washout Rate Location
				ANT		SEP		INF		LAT			
				A1	A2	S1	S2	I1	I2	L1	L2	AP	
1	30 F	Left anterior	29,216	N	N	N	N	N	N	N	N	N	—
2	33 M	Left anterior	27,750	N	N	N	N	N	N	N	N	N	—
3	58 M	Right lateral	25,560	N	N	N	N	N	N	N	N	N	DSW
4	29 M	Right paraseptal	43,340	N	N	N	N	N	N	N	N	N	—
5	16 M	Left anterior	18,480	N	N	N	N	N	N	N	N	N	DSW
6	46 M	Left anterior	24,310	N	N	N	N	N	N	N	N	N	—
7	50 M	Right lateral	35,200	N	N	N	N	N	N	N	N	N	—
8	33 F	Right lateral	23,288	T	T	T	N	T	N	N	N	N	A I
9	43 M	Right anterior paraseptal	34,980	N	N	N	N	N	N	N	N	N	—
10	41 M	Left posterior paraseptal	24,288	N	N	N	N	T	N	N	N	N	DSW
11	39 F	Left anterior	25,748	N	N	N	N	N	N	N	N	N	—
12	15 M	Right lateral	22,320	N	N	N	N	N	N	N	N	N	DSW
13	58 M	Left anterior	28,710	N	N	N	N	N	N	N	N	N	—
14	41 M	Right lateral	40,560	N	N	N	N	N	N	N	N	N	—
15	15 M	Left anterior	25,670	N	N	N	N	N	N	N	N	N	—
16	62 M	Left anterior	30,784	N	N	N	N	N	N	N	N	N	—
17	15 M	Right lateral	33,660	N	N	N	N	N	N	N	N	N	DSW
18	53 M	Left anterior	27,360	N	N	N	N	N	N	N	N	N	—
19	16 M	Left anterior	32,870	N	N	N	N	N	N	N	N	N	DSW
20	16 M	Right lateral	29,070	N	N	N	N	N	N	N	N	N	DSW

Abbreviations as in Table I.

GROUP WITH WOLFF-PARKINSON-WHITE SYNDROME (TABLE IV): Two of 20 patients had transient defects and the specificity (90%) was similar to that in the control group (p = not significant).

Location of transient defects in patients without coronary artery disease: In 2 patients with RBBB and a false-positive response, the transient defects were seen in the inferior and septal segments. In patients with RBBB plus left-axis deviation, transient defects were also frequently found in the inferior and septal segments. In those with LBBB, transient defects were frequently seen in the anterior, inferior and septal segments; in patients with right ventricular pacing, such defects were frequently found in the septal, inferior and apical segments.

Washout rate analysis: An abnormal washout rate was frequently found in regions that coincided with transient defects in patients with RBBB plus left-axis deviation, LBBB and right ventricular pacing. Diffuse slow washout was found in 8 of the 74 patients without coronary artery disease and with normal intraventricular conduction (11%), in 5 of 22 with RBBB (23%), in 2 of 10 with RBBB plus left-axis deviation (20%), in 1 of 10 with LBBB (10%), in 1 of 9 with right ventricular pacing (11%), and in 7 of 20 with WPW syndrome (35%). The incidence of diffuse slow washout in patients with WPW syndrome was higher than in the control group ($p < 0.05$), although the other groups showed no significant difference compared with control subjects.

DISCUSSION

The present study showed that the specificity of exercise thallium-201 emission computed tomography in patients with normal intraventricular conduction (control), RBBB, RBBB plus left-axis deviation, LBBB, right ventricular pacing, and WPW syndrome was 94,

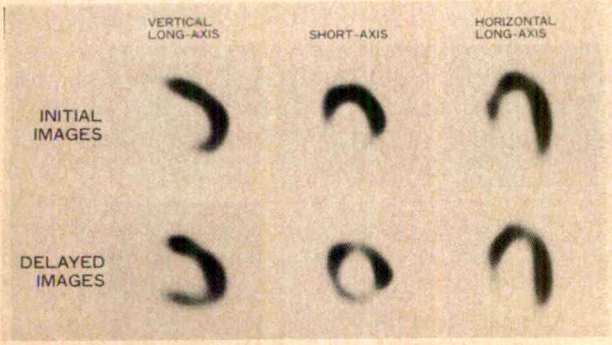


FIGURE 2. Exercise thallium study of patient 1 with right bundle branch block plus left-axis deviation, showing the initial and delayed images. The transient defects are visible in the septal and inferior segments.

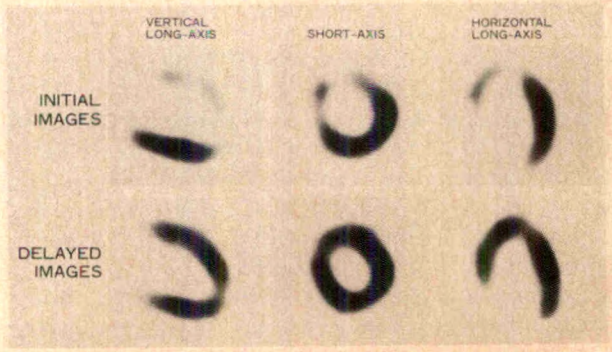


FIGURE 3. Exercise thallium study of patient 2 with left bundle branch block, showing the transient defects in the anterior, septal and apical segments.

86, 50, 30, 44 and 90%, respectively. Although there were no significant differences in specificity between group with RBBB and WPW, and the control group, the specificity in patients with RBBB plus left-axis deviation, LBBB or right ventricular pacing was significantly lower than in the control group.

Hirzel et al[9] studied 19 symptomatic patients with LBBB using thallium-201 planar imaging and indicated that reversible septal defects occurred in all 19 patients, but only 4 had left anterior coronary stenosis. Depuey et al[13] used thallium-201 emission computed tomography and found reversible or partially reversible septal perfusion abnormalities in 12 of 14 patients with LBBB undergoing coronary angiography, but only 3 of them had significant left anterior descending artery stenosis. The specificity in our patients with LBBB and right ventricular pacing was similar to that in these previous reports.

Archer et al[11] reported that ventricular preexcitation results in a high frequency of abnormal exercise thallium-201 planar imaging. In our study, only 2 of 20 patients with WPW syndrome had a transient defect with delayed thallium-201 washout. It is interesting that the location of the bypass tracts in our patients was the same as in those reported by Archer et al, and that diffuse slow washout was also frequently recognized.

To our knowledge, there are no prior reports that demonstrate the specificity of exercise thallium-201 testing in patients with RBBB plus left-axis deviation. The present study showed that it was low despite of high specificity in patients with RBBB. In other words, left anterior fascicular block in addition to RBBB may result in a decrease in specificity for diagnosing epicardial coronary narrowing.

The mechanisms producing transient defects in patients with intraventricular conduction disturbances were not elucidated by our study. However, they are speculated to be (1) functional ischemia as a consequence of asynchronous contraction, and (2) exercise-induced ischemia associated with small-vessel disease concomitant with fibrodegenerative changes.[14] By measuring regional myocardial blood flow in dogs using strontium-85 and chromium-51-labeled microspheres, Hirzel et al[9] documented that during LBBB induced by right ventricular pacing, there was a 26% reduction in blood flow in the septum compared with the lateral wall. They speculated that the decrease in septal perfusion may result from compression of septal arteries by the myocardium as a consequence of asynchronous septal contraction. However, transient defects in our study were found in more extensive regions and the perfusion abnormalities of the other segments could not be explained simply by asynchronous contraction. In addition, Jazmati et al[15] recently demonstrated a low prevalence (14%) of septal defects and a high prevalence of defects in other regions in 93 unselected patients with LBBB who underwent exercise thallium-201 myocardial imaging. Therefore, we consider that exercise-induced ischemia may be due, in large part, to small-vessel disease associated with fibrodegenerative changes that might cause intraventricular conduction disturbances. The extent of fibrodegenerative changes in patients with LBBB or RBBB plus left-axis deviation could be greater than in patients with RBBB, and this may be the reason why the incidence of transient defects in patients with LBBB, right ventricular pacing, or RBBB plus left-axis deviation was higher than in patients with RBBB. In addition, patients with mild or early idiopathic cardiomyopathy might have been included in our study group, because exclusion criteria were an echocardiographic left ventricular ejection fraction <50% and a wall thickness >15 mm. Therefore, thallium-201 perfusion abnormalities may have been due to underlying heart disease rather than to intraventricular conduction disturbances itself, although they have been augmented by asynchronous contraction.

In an effort to improve its sensitivity and specificity for detecting coronary artery disease, measurements of regional myocardial thallium-201 clearance (washout rate) have been adopted as an adjunct to the qualitative or quantitative assessment of regional defects in thallium uptake. Therefore, defects associated with artifact such as breast attenuation are excluded. However, diffuse slow washout may be associated not only with exercise performance but also with other factors.[16,17] In patients with WPW syndrome, diffuse slow washout is frequently recognized despite good exercise performance and the mechanism remains unknown.

Study limitations: Because the present study was retrospective except in the WPW group, the study group may have been affected by various biases. Also, patients with RBBB and WPW syndrome could not all undergo coronary angiography. However, patients with WPW syndrome were relatively young and had no angina or equivalent symptoms. In addition, because the sensitivity of exercise thallium-201 emission computed tomography was high, the incidence of false-negative responses was low in patients with RBBB and WPW syndrome who underwent no coronary angiography and had no perfusion defects. Furthermore, the purpose of the present study was to assess the false-positive rate in patients with various types of intraventricular conduction disturbances rather than the sensitivity of this method.

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Effects of Enalapril on Long-Term Mortality in Severe Congestive Heart Failure

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All surviving patients in a double-blind study comparing the effects of enalapril and placebo on survival in severe congestive heart failure were recommended to be treated with active drug after stopping the trial. Two-year follow-up from the end of the blinded trial demonstrated that among 77 survivors of 127 patients originally allocated to the group with enalapril, 38 were still alive. Of 126 patients allocated to the group with placebo 58 survived the blinded study, and after 2-year follow-up 26 were still alive. Thus, the difference between the original treatment groups remained, despite that treatment with enalapril was made available to all surviving patients and that those in the group with enalapril were sicker at baseline than those in the group with placebo. If enalapril was prescribed, the mortality was 47% compared with 75% if it was not. Life-table analysis suggests a marked carry-over effect of treatment in the group with enalapril that lasted for up to 15 months before mortality rates became comparable in the 2 treatment groups. This strongly suggests that enalapril confers structural protection to the failing myocardium.

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We recently demonstrated that the short-term mortality in patients with severe congestive heart failure (CHF) can be reduced by 40% with enalapril when added to optimal treatment with diuretics, digitalis and vasodilators other than angiotensin-converting enzyme inhibitors.[1] The study was stopped prematurely by the safety committee to allow all remaining patients the benefit of treatment.

The improved survival observed with enalapril was primarily achieved owing to the reduction in death due to progressive CHF. The effect of enalapril was almost exclusively observed among patients with marked neurohormonal activation.[2] To examine if treatment is restricted to the time of inhibition of neurohormonal activation or if long-term treatment also confers a longer lasting protection to the myocardium, follow-up on mortality was obtained for all patients participating in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) after the trial was stopped. If a long-lasting effect is conferred on the myocardium by enalapril, we may anticipate a catch-up time before the 2 treatment groups attain the same risk. Conversely, if the reduction of the neurohormonal activation is the primary mechanism and is not related to structural changes in the heart and the peripheral circulation, a short catch-up time is assumed. This report includes 2-year follow-up of all patients alive when the double-blind trial period with enalapril and matching placebo was terminated, and all patients were offered treatment with enalapril.

METHODS

The CONSENSUS trial included 253 patients (mean age 70 years, range 36 to 91) with severe CHF (New York Heart Association class IV) from 35 hospitals in Norway, Sweden and Finland. Patients were randomized to enalapril or identical placebo in a blinded, randomized fashion. Details of the inclusion procedure and results were previously presented.[1] Coronary artery disease was a major cause of CHF in 73% of the patients, dilated cardiomyopathy in 15%, valvular heart disease in 22%, and hypertension in 21%. All patients were on diuretics (mean furosemide dose 219 mg); 94% were on digitalis, whereas 50% received vasodilators (mostly isosorbide dinitrate, except angiotensin-converting enzyme inhibitors). The treatment dose of enalapril/placebo was 2.5 to 40 mg/day. This dose was titrated during the initial 3 weeks, and the average daily dose of enalapril was 18.4 mg. The mortality calculated

TABLE I Follow-Up of Patients Alive from December 15, 1986, to December 15, 1988

	Original Allocation Groups		
	Placebo	Enalapril	p Value
Survivors at end of blind study	58	77	<0.003
Survivors at end of follow-up	26	38	<0.006
Deaths	32 (55%)	39 (51%)	
Treated with enalapril	39	68	
Deaths	18 (46%)	32 (47%)	
Not treated with enalapril	19	9	
Deaths	14 (74%)	7 (78%)	

from life-table analysis was 48% at 6 months (primary objective) in the placebo group and reduced by 40% to 29% in the enalapril group. The CONSENSUS trial was stopped prematurely by the ethical review committee on December 14, 1986, after an average observation period of 6 months, and the mortality of the patients in that study, from enrollment to that date, was previously reported.[1-3] After the study was stopped, the blind was broken for all patients, and the investigators were encouraged to treat all surviving patients with enalapril or other angiotensin-converting enzyme inhibitors. A follow-up questionnaire was obtained from all 35 participating centers on patients alive when the CONSENSUS trial was terminated. Information on survival and use of enalapril was retrieved for all patients from December 14, 1986, to December 15, 1988, which was 2 years after the end of the original trial, and this report contains an analysis of those data. Follow-up data on surviving patients were analyzed according to the original randomization schedule. The actual mortality of the groups was calculated beginning on December 15, 1986, from the follow-up data alone, but no statistical tests were performed on these data, because the groups were not comparable at the time the CONSENSUS trial was stopped. A second analysis combined the follow-up with the original data, essentially ignoring the fact that the code was broken, and the treatments were altered. Life-table curves according to Kaplan-Meier[4] were calculated. The curves were compared using log-rank statistics.[5]

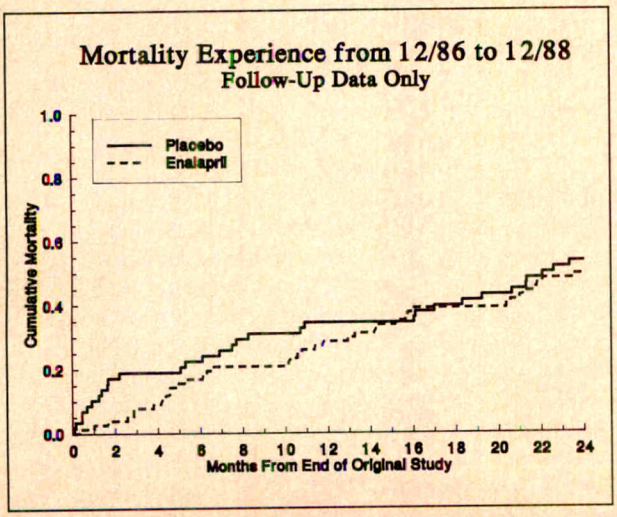


FIGURE 1. Cumulative mortality during follow-up from December 15, 1986, when CONSENSUS trial was stopped, to December 15, 1988, according to original allocation group.

RESULTS

In the CONSENSUS trial, 58 of 126 patients randomized to placebo survived through December 14, 1986, and 77 of 127 patients randomized to enalapril survived through the same date. Therefore, there were a total of 135 surviving patients with additional follow-up of 2 years. The mortality of these 135 patients is shown in Figure 1 and listed in Table I. Thirty-two of the 58 (55%) patients with placebo died, and 39 of the 77 (51%) patients with enalapril died. In the placebo group, 39 of 58 surviving patients began with enalapril, and 9 of these discontinued enalapril for unknown reasons during follow-up. In the enalapril group, 68 of 77 patients continued enalapril, and 8 of these discontinued treatment during follow-up. It is not fair to compare the groups based on their actual treatments, because in most cases the decision to use enalapril was based on the patient's condition. However, it is still interesting to see whether the results based on actual therapies are consistent with our expectations. In the enalapril group, the mortality rate among patients not receiving enalapril was 78% (7 of 9) compared with 47% (32 of 68) for those receiving enalapril. In the placebo group, the mortality rate among patients not receiving enalapril was 74% (14 of 19) compared with 46% (18 of 39) for those receiving enalapril (Table I).

The actual mortality curves for all surviving patients according to their original allocation group after the CONSENSUS trial was stopped are shown in Figure 1. All patients were offered treatment with enalapril. The results show that the enalapril group had a lower mortality rate than the placebo group had during the first 12 to 15 months after the end of the blinded trial. After 15 months, the 2 groups merge with a similar mortality rate. At 3 months, the predicted mortality in the placebo group was 19% compared with 8% in the enalapril group, whereas at 18 months, the mortality rates were virtually the same (40% in the placebo vs 39% in the enalapril group). Comparison of baseline characteristics of patients surviving the CONSENSUS trial showed that the 2 groups were different at baseline. Surviving patients receiving enalapril were generally sicker (higher serum creatinine and neurohormone levels, and larger heart size) (Table II).

Figure 2 illustrates the accumulated mortality for all patients included in the CONSENSUS trial, including both the original and 2-year follow-up data, and ignoring the fact that the blind code was broken and the treatments were altered on December 15, 1986. The curves are significantly different ($p = 0.006$). Throughout the entire follow-up, the percent reduction in mortality due to enalapril was estimated to be approximately the same with the combined data as with the original data alone (Table III). Essentially, a similar treatment effect was obtained in subgroups of patients with and without valvular heart disease (Figure 3, A and B).

TABLE II Baseline Characteristics of the CONSENSUS Patients

	All Patients		Surviving Patients on 12/14/86	
	Enalapril n (mean)	Placebo n (mean)	Enalapril n (mean)	Placebo n (mean)
Age (yrs)	127 (70.6)	126 (69.7)	77 (69.9)	58 (70.3)
Systolic BP	127 (121.7)	126 (122.8)	77 (121.9)	58 (125.6)
Diastolic BP	127 (77.1)	125 (76.1)	77 (77.4)	58 (76.8)
Heart rate	126 (79.8)	123 (81.2)	77 (80.9)	57 (78.8)
Creatinine	127 (132.0)	124 (124.1)	77 (131.1)	58 (119.1)
Heart size	124 (873.5)	120 (865.0)	75 (900.0)	56 (876.9)
A II	120 (68.3)	119 (76.0)	73 (69.5)	57 (65.2)
ALDO	119 (1,435)	119 (1,330)	73 (1,517)	57 (1,110)
ANP	114 (520.7)	112 (404.7)	69 (471.1)	55 (324.5)
NA	114 (909.3)	116 (934.9)	67 (905.8)	56 (736.8)

A II = angiotensin II; ALDO = aldosterone; ANP = atrial natriuretic peptide; BP = blood pressure; NA = noradrenaline.

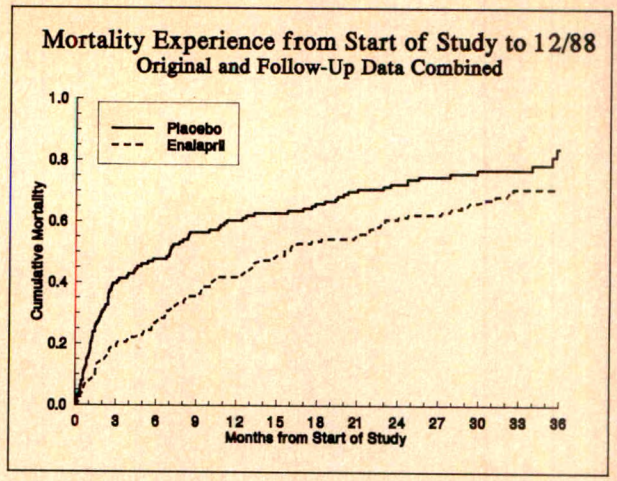


FIGURE 2. Life-table curves with monthly changes using combined follow-up and original data. Original allocation groups are presented.

DISCUSSION

Long-term follow-up of the patients from the CONSENSUS trial showed that the benefit of enalapril to mortality compared with that of placebo continued >1 year after treatment with enalapril was offered to all patients. The difference in number of deaths after 3 years was still significantly lower among patients originally randomized to enalapril. In the original CONSENSUS trial, the 2 study groups were comparable at baseline with respect to all vital and high-risk variables. It was important for the follow-up that the 2 groups were not comparable when the study was unblinded. Because of a higher death rate among the patients with placebo, more high-risk patients remained in the enalapril than in the placebo group at the end of the study (Table II). A comparison of baseline characteristics reveals that the remaining patients in the placebo group were slightly better at baseline with respect to high-risk variables like noradrenalin, aldosterone, heart size and creatinine. It was expected that these combined curves would not be as separate as the original curves, because the placebo group had been "contaminated" by data from patients actually receiving angiotensin-converting enzyme inhibitors. However, the finding that combined curves were still clearly separate (Figure 2) strengthens the conclusion of enalapril's efficacy.[1] The effect of enalapril on mortality in the blinded CONSENSUS trial began early, and in this respect the 2 groups were significantly different as early as 2 months after randomization.

Because all patients had the same choice of therapies available during follow-up, the only difference between the treatment groups in the analysis of follow-up data alone was the therapy before the beginning of follow-up. Therefore, overlapping mortality curves would have suggested that the full effect of enalapril was achieved immediately, because patients who were previously receiving enalapril were no better off than those just beginning enalapril therapy. The fact that the mortality curves during follow-up continued to favor the enalapril group strongly suggests that it takes time to obtain the full benefit of enalapril therapy, and strengthens the original results of the CONSENSUS trial.[1] The weakness of this analysis, however, is that the treatment groups were not comparable. However, the enalapril group contained patients sicker at baseline who survived during the study period. The previous placebo groups

TABLE III Comparison of Combined and Original Mortality Curves

	Combined Data (%)			Original Data (%)		
Follow-Up (mos)	Placebo Mortality	Enalapril Mortality	Reduction Due to Enalapril	Placebo Mortality	Enalapril Mortality	Reduction Due to Enalapril
1	17	8	53	16	8	50
2	31	15	52	30	16	55
3	34	19	53	40	19	51
4	43	22	49	42	22	48
5	46	24	48	46	24	48
6	48	28	42	48	29	40
7	50	31	38	52	31	41
8	54	33	39	56	33	40
9	56	36	36	60	37	38
10	57	39	32	61	41	33
11	60	42	30	63	46	28
12	60	42	30	63	46	28

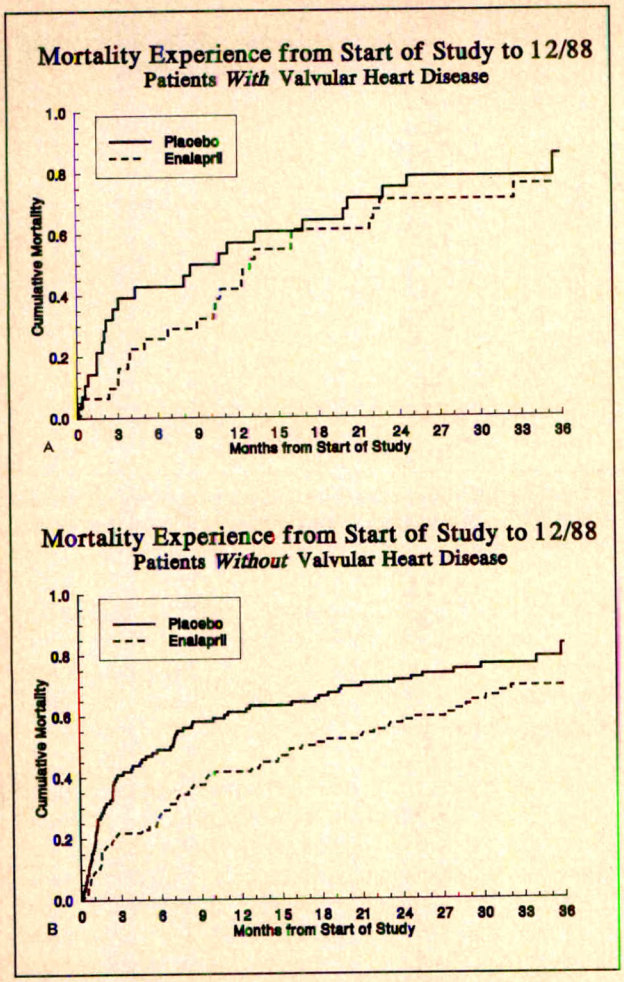


FIGURE 3. Cumulative mortality for subgroups of patients with *(A)* and without *(B)* valvular heart disease. Life-table curves with monthly changes using combined follow-up and original data. Original allocation groups are presented.

included lower risk patients who survived while not receiving enalapril, which would be a negative bias. Therefore, parallel curves after all patients were unblinded (Figure 2) suggest a differential effect on the myocardium obtained by treatment during the blinded placebo-controlled study.

By comparing the 2 mortality curves (Figure 2) according to the original allocation group at randomization (intention to treat) it may be surmised that long-term treatment with enalapril prolonged the life of severely ill patients by >1 year.

The mechanisms of protection by enalapril are as yet undefined. Angiotensin-converting enzyme inhibitors in CHF have been shown to improve hemodynamics and to prevent diastolic and systolic dysfunctions of the left ventricle.[6,7] The CONSENSUS trial demonstrated a significant reduction in heart size (10%) among patients receiving enalapril compared with no change in the placebo group.[1] Reduction of wall stress by reduction of afterload, as well as of preload, may prevent long-term circumferential dilatation of the heart that otherwise may presage death in CHF.[8] Myocardial hypertrophy was shown to regress during angiotensin-converting enzyme inhibition,[9,10] which may preclude the risk associated with myocardial hypertrophy.[11]

Death due to progression of CHF is clearly associated with excessive neurohormonal activation.[2,12] Enalapril effectively reverses overall neurohormonal activation parallel to a reduction in mortality.[2] Essentially similar effects of treatment were observed in subgroups of different etiology. This suggests that unloading of the left ventricle is a principal mechanism of effect in CHF.

Unloading of the failing ventricle, and regression of myocardial hypertrophy, along with blocking of neurohormonal effects on the myocardial circulation and metabolism, may improve the supply/demand ratio of the myocardium and prevent structural changes of the myocardium that may cause progression of CHF.

The present study demonstrates that long-term treatment with enalapril confers long-lasting myocardial protection. The marked carry-over effect observed during follow-up was also recognized in time-mortality curves among patients who were withdrawn from the blinded CONSENSUS trial.[1] Although all patients who discontinued blinded treatment in the CONSENSUS trial had a higher mortality than those who continued to receive test medication, those in the enalapril group who discontinued treatment lived 3 times longer than those withdrawn from placebo treatment.[1]

APPENDIX

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Left Ventricular Filling and Ventricular Diastolic Performance After Percutaneous Balloon Mitral Valvotomy

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The time course of left ventricular (LV) filling and LV diastolic performance were examined in 27 consecutive patients in sinus rhythm before and acutely after balloon mitral valvotomy (BMV). The mitral valve area acutely increased from 1.1 ± 0.3 to 2.1 ± 0.8 cm^2. Simultaneous pressure-volume data were obtained using digital subtraction left ventriculography and LV micromanometer pressure before and 10 minutes after BMV. The time constant of LV isovolumic relaxation was unchanged after BMV (50 ± 10 ms before BMV vs 47 ± 13 ms after BMV). In addition, values before and after BMV for LV end-diastolic volume (123 ± 29 vs 125 ± 36 ml), end-diastolic pressure (11 ± 4 vs 12 ± 4 mm Hg) and diastolic filling time (337 ± 126 vs 338 ± 152 ms) were not altered by the procedure. After BMV the peak diastolic filling rate (403 ± 143 vs 469 ± 302 ml/s) was maintained despite a 36% reduction in left atrial filling pressure. There was a trend toward earlier occurrence of the peak filling rate (196 ± 127 vs 146 ± 148 ms, p = 0.08). The percentage of diastolic filling in the first third of diastole, however, was similar (42 ± 9 vs 48 ± 16%) before and after the procedure.

Thus, the time course of LV filling is not significantly altered acutely after BMV, but is maintained at reduced left atrial filling pressure. Neither LV relaxation or LV chamber compliance are altered acutely after BMV. Changes in LV diastolic performance, which have recently been shown to alter Doppler mitral valve half-time measurements independent of changes in valve area, do not contribute to the decreased correlation between Doppler and invasive data observed acutely after BMV. In addition, the lack of impairment of LV isovolumic relaxation suggests that LV ischemia or papillary muscle injury are unlikely to contribute to increased mitral regurgitation after BMV.

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Over the last few years, percutaneous balloon mitral valvotomy (BMV) has been shown to be an effective treatment for selected patients with symptomatic mitral valve stenosis, resulting in immediate reduction of the mitral valve gradient and clinical improvement.[1–5] Several questions related to the immediate results of the procedure, however, remain undefined. Impaired left ventricular (LV) diastolic filling is the critical pathophysiologic abnormality in mitral stenosis. LV filling in mitral stenosis is complex and is dependent on the interaction between left atrial pressure, mitral valve function, diastolic filling time, and the diastolic performance of the left ventricle. Whereas the time course of LV filling is known to be abnormal in mitral stenosis,[6] the filling characteristics of the left ventricle after BMV have not been examined.

In addition, evaluation of the immediate results of the procedure has been complicated by the poor correlation between the hemodynamic and Doppler data obtained acutely after BMV.[7–10] Thomas et al[10] suggested that this discrepancy may be in part related to acute alteration of the diastolic performance of the left ventricle after BMV, thus affecting the Doppler half-time measurements. Aortic balloon valvuloplasty has been shown to acutely impair LV diastolic performance.[11] LV isovolumic relaxation and LV chamber compliance may be altered by LV ischemia or myocardial trauma, or both, during BMV, and thereby alter Doppler half-time measurements independent of actual change in mitral valve area.[10,12,13]

Finally, transient papillary muscle dysfunction, resulting from either localized LV trauma or ischemia, has been considered a cause of increased mitral regurgitation complicating BMV, implying that the severity of mitral regurgitation complicating BMV may decrease with time.[14] Study of LV diastolic performance after BMV should be useful in examining this hypothesis. Ischemia itself, or asynchrony resulting from such regional LV dysfunction, impairs isovolumic relaxation resulting in prolongation of the time constant of isovolumic relaxation (tau).[15,16] Thus, examination of tau be-

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fore and after the procedure, in cases of increased mitral regurgitation, should permit investigation of this hypothesis.

This study examines the magnitude and time course of LV filling, and defines LV diastolic function before and immediately after BMV.

METHODS

Patient group: From January 1989 to October 1990, 27 consecutive patients (24 women and 3 men, mean age 44 ± 11 years [range 26 to 68]) in sinus rhythm underwent percutaneous BMV. All patients gave informed consent in a protocol previously approved by the human investigations review board. Selection for BMV was based on clinical and echocardiographic evaluation. Patients with moderate or severe mitral regurgitation, significant calcification of the valve, or evidence of left atrial thrombus were excluded.

Balloon mitral valvotomy procedure: Right- and left-sided cardiac catheterization was performed through the left femoral vessels. Transeptal catheterization was performed from the right femoral vein using the Brockenbrough technique. Balloon dilation of the mitral valve was accomplished in 20 patients with the double balloon technique (Mansfield Inc., Watertown, Massachusetts) and in the other 7 patients with the Inoue balloon catheter system (Toray Industries, Tokyo, Japan).[1,17]

Hemodynamic evaluation: Before and after BMV, right- and left-sided cardiac pressures and the mitral valve gradient were measured. The mean mitral valve gradient was determined from planimetry of simultaneous left atrial and LV pressure recordings. Cardiac output was measured in 19 patients using the Fick method and in 8 patients using thermodilution. Mitral valve areas were determined using the Gorlin formula.[18] Oximetry, to evaluate left to right shunting, was performed after BMV. Supravalvular aortography and coronary arteriography were performed in the initial assessment of patients before BMV. Twenty-one patients had no aortic regurgitation, whereas 6 had 1+ aortic insufficiency. None had coronary artery disease.

Pressure-volume loops were obtained using R-wave gated digital subtraction left ventriculography (ADAC 4100c, Milpitas, California) coupled to simultaneous digitized LV micromanometer pressure (Millar Instruments, Houston, Texas). Left ventriculography was performed during injection of nonionic contrast, 40 ml at 10 ml/s (iohexol, Winthrop Pharmaceuticals or iopamidol, Squibb Inc.). Digital ventriculographic images were recorded at 30 frames/s and simultaneous LV pressures were digitized at 5 ms intervals. LV volumes were calculated using the area-length method and were corrected using a regression defined in this laboratory from 20 human LV casts of known volume [true volume(ml) = 0.60 · calculated volume(ml) + 11.6 ml].

Determination of the time constant of isovolumic relaxation: The decrease in LV pressure (P) during isovolumic relaxation as function of time (t) was mathematically modeled by the negative exponential function ($P = P_0 \cdot e^{-t/\tau}$) as described by Weiss et al.[19] The time period of isovolumic relaxation was defined from the time of the minimum first time derivative of LV pressure until the time when LV pressure was 5 mm Hg more than LV end-diastolic pressure.[19] Solution of the equation for tau (τ), the time constant of isovolumic relaxation, was performed by determining the relation of the natural logarithm of LV pressure during isovolumic relaxation versus time. The slope (m) of this relation is related as: $m = -1/\tau$.

Determination of diastolic filling and passive left ventricular diastolic function: LV diastolic filling was defined from the minimum volume to the end-diastolic volume. End-diastole was defined at the time of the electrocardiographic R wave. The LV volume curve during diastolic filling was smoothed using a 7 point smoothing function.[20] LV diastolic volume curve was examined to determine peak filling rate; the maximum value of the first time derivative of the volume curve. The time from the start of diastolic filling to the time of the peak filling rate was also determined. The total diastolic filling time was recorded from the beginning of LV filling to end-diastole and the percentage of diastolic filling that occurred in the first third of diastole was determined. The passive diastolic properties of the left ventricle were defined by the end-diastolic parameters of LV pressure and volume, measured at the time of the electrocardiographic R wave.

Statistical analysis: Data are expressed as mean ± standard deviation unless otherwise stated. The significance of continuous variables was tested using the Wilcoxon rank sum test and the Mann-Whitney test for paired and nonpaired data, respectively. A value of $p < 0.05$ was considered statistically significant. Linear regression was used to test the validity of the mathematic model used to calculate tau.

RESULTS

Results of balloon mitral valvotomy: After BMV, mean mitral valve gradient decreased from 11 ± 5 to 5 ± 3 mm Hg ($p < 0.0001$). Cardiac output was unchanged. Mitral valve area increased from 1.1 ± 0.3 to 2.1 ± 0.8 cm^2 ($p < 0.0001$). Mean left atrial pressure decreased from 22 ± 5 to 14 ± 5 mm Hg ($p < 0.0001$), while mean right atrial pressure was unchanged (6 ± 4 mm Hg before vs 6 ± 4 mm Hg after BMV).

There was no difference in the mitral valve area achieved in the 19 patients using the double balloon technique (2.1 ± 0.8 cm^2) and the results obtained in the 7 patients using the Inoue balloon catheter (1.9 ± 0.5 cm^2). A left to right shunt after BMV (defined as pulmonary to systemic flow ≥1.5 to 1) was detected in 6 patients. The severity of mitral regurgitation, on an ordinal scale, increased from 0.5 ± 0.6 before to 1.0 ± 1.1 after BMV ($p = 0.02$). Mitral regurgitation increased in 10 of the 27 patients (Table I).

Left ventricular diastolic filling: Despite the decrease in left atrial filling pressure, the peak mitral valve filling rate was similar before and after BMV (403 ± 143 ml/s before vs 469 ± 302 ml/s after BMV). There was a trend toward the peak filling rate occurring earlier in diastole (196 ± 127 ms before vs 146 ± 148 ms after BMV, $p = 0.08$). The percentage of early diastolic filling (occurring in the first third of dias-

TABLE I Effect of Balloon Mitral Valvotomy on Left Ventricular Filling and Diastolic Function

Pt. No.*	MVA		LAP		ED Fil		EDV		EDP		tau		MR	
	pr	po	pr	po	pr	po	pr	po	pr	po	pr	po	pr	po
1	1.1	4.1	30	12	39	50	160	145	12	12	46	38	0	0
2	0.9	2.7	24	15	39	64	85	82	12	10	63	51	0	1
3	1.4	4.1	18	5	50	20	115	101	8	5	49	42	0	0
4	1.0	2.7	22	5	57	64	133	132	13	6	32	27	0	1
5	0.7	1.8	22	15	53	40	130	146	12	10	61	66	0	1
6	1.4	3.5	19	15	46	42	118	115	10	15	54	54	1	0
7	0.7	1.7	16	12	19	44	122	150	10	10	50	60	2	4
8	0.9	2.1	20	13	52	81	122	125	13	16	56	58	0	0
9	0.7	1.6	18	14	44	53	166	164	14	17	60	56	1	1
10	0.9	1.9	22	15	30	49	109	143	13	13	61	74	0	0
11	0.9	1.8	22	14	48	52	109	74	7	8	46	38	2	2
12	0.8	1.6	29	10	39	37	89	70	6	8	52	42	1	0
13	1.4	2.8	18	17	40	28	158	155	18	17	64	72	0	2
14	0.8	1.5	35	30	41	32	68	70	9	15	40	35	0	4
15	1.0	1.8	18	14	53	59	125	121	6	10	33	32	0	1
16	1.2	2.1	17	12	43	41	116	118	14	13	56	49	1	1
17	1.2	2.0	24	17	58	64	116	124	14	15	54	59	0	0
18	0.7	1.1	29	14	35	27	146	130	6	6	36	44	1	1
19	1.1	1.7	21	21	44	62	130	166	15	18	62	58	0	2
20	1.0	1.5	26	14	44	74	130	166	17	20	62	41	1	1
21	1.1	1.6	24	14	31	41	118	108	6	8	46	41	0	0
22	1.1	1.6	24	20	36	49	107	99	7	18	39	31	1	2
23	1.7	2.4	21	12	27	52	127	118	8	8	43	43	0	0
24	1.4	1.9	22	11	52	31	109	127	12	10	45	40	0	0
25	1.6	2.1	20	13	38	24	117	108	12	10	45	42	1	1
26	1.3	1.4	18	13	37	76	218	238	11	11	40	36	0	1
27	1.6	1.6	14	20	39	38	92	85	5	5	44	30	1	1
Mean	1.1	2.1	22	14	42	48	124	125	11	12	50	47	0.5	1.0
± SD	±0.3	±0.8	±5	±5	±9	±16	±29	±36	±4	±4	±10	±13	±0.6	±1.1
p Value	†		†										‡	

*Patients arranged in descending order based on percent increase in mitral valve area.
†p = 0.0001; ‡p = 0.02.
ED Fil = early diastolic filling (percent of diastolic filling in the first third of diastole); EDP = end-diastolic pressure (mm Hg); EDV = end-diastolic volume (ml); LAP = left atrial pressure (mm Hg); MR = mitral regurgitation (angiographic ordinate scale); MVA = mitral valve area (cm^2); pr = before balloon mitral valvotomy; po = after balloon mitral valvotomy; p value = not significant unless specified; tau = time constant of isovolumic pressure decline (ms).

tole), however, was similar before and after BMV (Table I). Heart rate (73 ± 14 beats/min before vs 75 ± 16 beats/min after BMV) and diastolic filling time (337 ± 126 ms before vs 338 ± 152 ms after BMV) were unchanged.

Measures of left ventricular diastolic function: Tau was unchanged after BMV: 50 ± 10 ms before vs 47 ± 13 ms after BMV. The negative exponential model of isovolumic relaxation fit closely with the measured LV pressure decay. The relation of the natural logarithm of LV pressure versus time was linear ($r = -0.996$). In addition, the change in tau in the 10 patients with an increase in mitral regurgitation after BMV (−2 ± 7 ms) was not different than the change in tau in the 17 patients with no increase in mitral regurgitation (−3 ± 8 ms).

The passive diastolic properties of the left ventricle were similarly unchanged after BMV (Table I). LV end-diastolic pressure and LV end-diastolic volume and diastolic filling period were similar before and after BMV indicating that passive LV diastolic pressure-volume relations were unchanged after BMV.

DISCUSSION

Filling characteristics of the left ventricle after balloon mitral valvotomy: Mitral valve stenosis impedes LV filling. In these patients, the early rapid filling portion of the LV filling curve is blunted and the relation of LV volume as a function of time during diastolic filling is nearly linear.[6] After BMV one might expect an increase in early diastolic filling, approaching a more normal filling pattern and an increase in the magnitude of total diastolic filling.[10] Whereas this study demonstrates a trend toward earlier occurrence of the peak diastolic filling rate after BMV, the time course of diastolic LV filling is not significantly altered acutely after BMV, because a similar percentage of filling occurred during the early rapid filling phase (first third) of diastole before and after BMV. The lack of significant change in the time course of diastolic filling may be related to inadequate improvement in mitral valve mobility after BMV. This finding, however, may also be related to the fact that the time course of LV filling is also governed by the diastolic properties of the left ventricle, which in this study were not acutely altered by the procedure. Whether early diastolic filling improves in late follow-up after BMV was not addressed by this study and requires further investigation.

The total magnitude of diastolic venticular filling and LV end-diastolic volume were also similar before and immediately after BMV. The end-diastolic volume of the ventricle is primarily determined by the diastolic properties of the ventricle itself. Without an acute volume load on the ventricle, such as the creation of severe

mitral regurgitation, it is unlikely that LV end-diastolic volume would increase acutely after BMV. The primary hemodynamic finding in the present study is that the magnitude and time course of LV filling are maintained despite the significant reduction in left atrial filling pressure. This finding is in accord with improvements in exercise hemodynamics demonstrating a significant reduction in pulmonary capillary wedge pressure at similar work loads after BMV.[21]

Left ventricular isovolumic relaxation after balloon mitral valvotomy: The energy-requiring process of isovolumic relaxation is not impaired immediately after BMV. Isovolumic relaxation is particularly sensitive to LV ischemia and results in a prolongation of tau.[15,16] Whereas balloon aortic valvuloplasty causes LV ischemia and a prolongation of tau,[11,22] tau is unchanged after the episodes of systemic hypotension that occur with balloon inflation during BMV. The tenuous coronary flow in patients with aortic stenosis likely contributes to the differing effects of the 2 procedures on LV isovolumic relaxation. Balloon inflation during aortic valvuloplasty occludes LV outflow resulting in a profound increase in LV pressure and myocardial oxygen demand, while at the same time partially occluding flow into the coronary ostia. These events are not common to the BMV procedure.

Left ventricular chamber compliance after balloon mitral valvotomy: The mathematic model developed by Thomas et al[10] suggests that LV chamber compliance may be decreased acutely after BMV.[10] This model predicts that the compliance of LV myocardium is unchanged after BMV, but that LV chamber compliance is reduced, with the ventricle operating at larger end-diastolic volumes, on the stiffer portion of the diastolic pressure-volume curve. The present study, however, demonstrates that LV volumes and chamber compliance are not acutely altered by BMV. The similarity of LV chamber compliance is demonstrated by the measurements obtained at end-diastole. LV end-diastolic volume, end-diastolic pressure, diastolic filling time, and end-diastolic pressure-volume relation were unchanged after BMV.

Discrepancy between hemodynamic and Doppler data after balloon mitral valvotomy: Mathematic theory and in-vitro models have shown that the Doppler mitral valve half-time does not depend solely on the mitral valve area, as the empirically derived equation would predict.[23] In-vitro models and canine studies have demonstrated that, in addition to valve area, mitral valve half-time is also related to the net left atrial and LV compliance, the square root of the initial pressure gradient and the rate of LV isovolumic relaxation.[10,12,13]

The data in the present study demonstrate that there is no change in LV isovolumic relaxation or LV chamber compliance after BMV. This and previous studies have shown a decrease in the initial mitral valve pressure gradient immediately after BMV. An increase in left atrial chamber compliance can be inferred from the present study and from the work of other investigators showing a reduction of left atrial pressure and chamber dimensions after BMV.[8,10] Thus, although the present study demonstrates that LV relaxation and LV chamber compliance are unchanged after BMV, the balance between the initial mitral valve gradient and left atrial chamber compliance may be acutely altered, thereby altering the Doppler half-time measurements independent of change in mitral valve area.

In addition, errors inherent to the hemodynamic calculation of the mitral valve area using the Gorlin equation may contribute to the discrepancy between hemodynamic and Doppler-derived valve areas acutely after BMV. Similar to the Doppler half-time "constant," the Gorlin constant has been shown to vary with cardiac output, being dependent on the pressure gradient across the valve.[24,25] In addition, measurement of cardiac output is made more difficult after BMV because of the possible creation of a left to right atrial level shunt. Whereas creation of a large shunt, as assessed by oximetry, is infrequent, transesophageal Doppler color flow imaging has demonstrated some degree of atrial level shunting in up to 87% of patients immediately after BMV.[26] Such small shunts could lead to errors in cardiac output measurements and subsequent errors in hemodynamic valve area calculations.

Etiology of increased mitral regurgitation after balloon mitral valvotomy: The severity of mitral regurgitation increased in 37% of patients in the present study. This is similar to previous studies, where a mild increase in the severity of mitral regurgitation has been observed in about one-half of patients after BMV.[8,14] At 6-month follow-up, however, these studies have shown a decrease in the severity of mitral regurgitation compared with observations made immediately after the procedure. This has led to the hypothesis that some cases of increased mitral regurgitation may be due to transient traumatic or ischemic papillary muscle dysfunction resulting from the procedure.[14]

In the present study, there was no evidence of impaired isovolumic relaxation (tau) in the group of patients with increased mitral regurgitation after BMV. Ischemic or traumatic papillary muscle dysfunction would be expected to cause asynchronous LV relaxation and a prolongation of tau. This study suggests that transient papillary muscle trauma or ischemia is not the cause of increased mitral regurgitation after BMV. Increased mitral regurgitation is most likely a result of damage to the valve itself, resulting from excessive commissural splitting, anterior leaflet prolapse, or creation of a tear in the valve leaflet. If not pronounced, mitral regurgitation due to the former 2 etiologies may improve with time.

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Cardiac Function After Domino-Donor Heart Transplantation

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A major limitation in cardiac transplantation is donor availability. A possible way to increase the supply of donor hearts is to use explanted hearts from patients undergoing heart-lung transplantation for primary lung disease. One potential advantage of this approach, termed domino-donor transplantation, is the existence of a donor right ventricle already adapted to pulmonary hypertension, which would therefore theoretically decrease the likelihood of acute donor right heart failure in recipients with preexisting elevation of pulmonary vascular resistance. Potential disadvantages include graft failure secondary to chronic effects of pulmonary hypertension on the right ventricle, arrhythmia and infections. Seven domino-donor transplants were performed at Stanford University Hospital; graft and patient survival to date are 100% at a mean follow-up of 20 months (range 1 to 26). Infection and rejection rates have been comparable to those of the current Stanford experience for conventional orthotopic transplantation. Right ventricular function and size have either improved or remained unchanged in all patients after transplantation. Transient early postoperative donor right ventricular dilation, a characteristic adaptive response seen in nondomino transplants, occurred in 4 patients with pulmonary hypertension before surgery. These data indicate that, with adequate assessment before surgery, domino-donor cardiac transplantation is an appropriate means of augmenting the donor pool.

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Combined heart-lung or lung transplantation is becoming increasingly accepted as therapy for treatment of patients with end-stage pulmonary hypertensive or parenchymal disease. Although patients with these conditions could theoretically be treated with a double lung transplant, reports from the Toronto Lung Transplant Group[1] indicate that there is significant risk of severe airway complications after this treatment. Therefore, many transplant centers offer combined heart-lung transplantation to selected patients with primary pulmonary hypertension, congenital cardiac conditions associated with Eisenmenger physiology, and end-stage pulmonary parenchymal diseases such as cystic fibrosis and bronchiectasis. The hearts of many of these patients developed adaptive changes with right ventricular (RV) hypertrophy secondary to chronic elevation of RV afterload as a consequence of pulmonary vascular disease. The heart from the explanted heart-lung block was not initially considered as donor material for transplantation. However, given limited donor availability it seemed reasonable to use some of these hearts as donors for transplantation, and successful application of this concept, called "domino-donor transplantation," was initially reported by Yacoub et al[4] in 1988.

Preexisting recipient pulmonary hypertension is a major cause of morbidity and mortality early after cardiac transplantation,[2] and complications are due to the inability of a normal donor right ventricle to acutely increase its external work load, leading to acute right heart failure immediately after surgery. Management of this complication is difficult and includes use of potent vasodilators such as nitroprusside and prostaglandin E_1. Irreversible pulmonary vascular disease secondary to chronic left ventricular (LV) failure has therefore been recognized as a contraindication to orthotopic cardiac transplantation, because of the increased risk of acute RV failure. Hence, a donor heart "preconditioned" with RV hypertrophy, but with preserved RV function, provides a theoretical advantage for patients with pulmonary hypertension and potentially allows them to be considered for orthotopic cardiac transplants that would otherwise be considered of excessively high risk. In the resulting domino-donor operation, a patient who is to receive a heart-lung transplant agrees to donate his/her heart with its preconditioned right ventricle to a patient who needs a heart transplant only.[3] In this report we examine the clinical and echocardiographic characteristics over time of a series of 7 recipients of such orthotopic domino-donor transplants. All 7 patients were considered acceptable recipients for orthotopic cardiac transplantation by our standard criteria.

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TABLE I Patient Demographics

Patient Pair	Age (yr) & Sex		Disease	
	Donor	Recipient	Donor	Recipient
1	30M	55M	CF	HC
2	28M	59F	CF	CAD
3	26M	24F	CF	HC
4	28M	48M	CF	DC
5	44M	50M	CF	DC
6	41F	57F	Bronchiectasis	CAD
7	44M	56M	α_1 Antitrypsin deficiency	CAD

CAD = coronary artery disease; CF = cystic fibrosis; DC = dilated cardiomyopathy; HC = hypertrophic cardiomyopathy.

METHODS

From April 1988 to May 1989, 7 domino-donor transplants were performed at Stanford University Hospital. Six recipients had follow-up care at Stanford; the seventh heart was harvested at Stanford and transplanted at another hospital where the recipient had follow-up.

Heart donors/heart-lung recipients: The primary diagnosis in the domino heart donors (mean age 34.3 years, range 26 to 44) was cystic fibrosis in 5 men, alpha-1 antitrypsin deficiency in 1 man, and severe congenital bronchiectasis in 1 woman.

Domino-donor heart assessment before transplantation: ECHOCARDIOGRAPHY: M-mode and 2-dimensional echocardiography were performed before surgery in all domino donors to assess cardiac structure and function. Quantitative measurement of RV size was not possible in 5 patients owing to technical difficulties in obtaining images from patients with severe pulmonary disease.

CONTRACTILITY: Qualitative assessment before surgery of 2-dimensional images revealed RV enlargement in 3 patients, and normal contractility in all domino-donor hearts. RV hypertrophy was present in 4 patients. LV size, wall thickness and function were normal before surgery in all patients, and all cardiac valves were normal in appearance and function.

CLINICAL FEATURES: None of the domino heart donors had severe RV heart failure before surgery, although 3 required diuretic therapy for control of peripheral edema.

All 7 domino donors were known to have chronic recurrent pulmonary infections that were controlled by frequent courses of antibiotic therapy; however, none had an active infection at the time of heart-lung transplantation and donation of the native heart.

Surgical procedure: The domino-donor hearts were matched to the recipients according to ABO compatibility and size in the usual fashion. The surgical technique was previously described.[4]

Heart recipients: Recipients of domino-donor hearts included 4 men and 3 women (mean age 49 years, range 24 to 57). The underlying disease process was coronary artery disease in 3 patients, idiopathic dilated cardiomyopathy in 2, and hypertrophic cardiomyopathy in 2. Clinical characteristics of the recipients and their donors are listed in Table I.

Six domino-donor orthotopic heart transplants were performed at Stanford University Hospital. Mean ischemic time for this group was 77.8 minutes (range 40 to 135). The remaining transplant was performed at another institution using a donor harvested at Stanford, with an ischemic time of 98 minutes.

Immunosuppression: Maintenance immunosuppressive therapy in all patients included cyclosporine (3 to 6 mg/kg/day), prednisone (0.1 to 0.6) and azathioprine (0.5 to 2). Induction therapy with murine monoclonal CD-3 antibody (OKT3) (5 mg/day for 14 days) was used in all patients, and total lymphoid irradiation (20 to 800 rad) was used in 3 as part of an experimental induction protocol. Acute rejection episodes were treated with augmentation of steroids with intravenous solumedrol (1 g/day for 3 days) or oral prednisone (100 mg/day for 3 days) for early or initial episodes diagnosed on RV biopsy, with rapid tapering to baseline dose during a 2- to 4-week period for later episodes. Steroid-resistant rejection was treated with a second course of OKT3 in OKT3 antibody-negative patients. Rejection that did not respond to these measures was treated on an experimental protocol with total lymphoid irradiation.

Follow-up: Patient follow-up included periodic visits with physical examination, chest x-ray, electrocardiogram and laboratory measurements of indexes of renal, hepatic and bone marrow function at 1- to 4-week intervals according to our current routine protocol. Graft function was assessed by serial echocardiography. Acute allograft rejection was monitored with the use of serial surveillance RV endomyocardial biopsy according to conventional protocol.

RESULTS

Survival: Follow-up ranged from 1.5 to 26 months, and no patient was lost to follow-up. All recipients of domino-donor hearts are alive. Figure 1 shows actuarial survival in domino-donor transplant patients compared with that in patients undergoing conventional orthotopic heart transplantation at Stanford during the same time period ($n = 80$) and demonstrates that survival is at least as good in the latter group.

Graft function: All patients had serial 2-dimensional echocardiograms after surgery; the results are listed in Table II with the recipient pulmonary vascular resistance values before treatment, and morphologic features of the donor right ventricle. Whenever possible, quantitative M-mode measurements were recorded.

All patients initially had normal LV size and function after surgery. Two patients later developed transient decrease in LV systolic function; this was clearly related to an episode of severe cellular rejection in 1 and was unexplained in the other. A third patient developed mild persistent global hypokinesis of the left ventricle after 6 episodes of cellular rejection. Abnormal septal motion was present in all donor hearts before transplantation and was frankly paradoxical in 5 cases. In all patients, the degree of abnormal septal motion decreased after transplantation, but did not fully return to normal. (Such septal motion abnormalities are very

TABLE II Right Heart Morphology and Hemodynamics of Domino-Donor Hearts

Pt. No.	Catheterization Data		Echocardiographic Data	
	PVR	PAS	RVE	RVH
Right Ventricular Morphology and Pulmonary Artery Pressures Before Transplantation				
1	2.5	23	–	–
2	1.4	24	–	–
3	2.3	40	–	–
4	2.1	32	+	–
5	2.1	49	+	+
6	2.1	38	+	+
7	1.7	33	+	–

Pt. No.	RVEDD Before Transplantation	RVEDD After Transplantation			
		Week 1	Week 2	Week 3	Week 4
Domino-Donor Right Ventricular Dimension by M-Mode Echocardiography Before and After Transplantation					
1	2.5	2.3	1.7	1.7	1.8
2	2.3	2.0	NA	NA	1.8
3	2.6	3.3	2.8	2.8	2.4
4	3.0	3.3	2.6	2.6	2.2
5	3.0	3.2	3.2	2.1	2.3
6	3.1	3.4	3.2	2.6	2.5
7	3.4	2.3	2.7	2.9	2.5

NA = not available; PAS = pulmonary artery systolic pressure (mm Hg; normal = 20 to 30); PVR = pulmonary vascular resistance (Wood units); RVE = right ventricular enlargement (defined as >3 cm increase in short-axis view); RVEDD = right ventricular end-diastolic dimension (M-mode echocardiography); RVH = right ventricular hypertrophy (defined as wall thickness >1 cm by M-mode or 2-dimensional echocardiography); + = present; – = absent.

common after transplantation and were not thought to be an unusual finding in these patients.)

RV size and function after transplantation was assessed in all patients and compared with data before transplantation when the heart was in situ in the domino donor (Table II). Pulmonary vascular resistances before surgery are presented for comparison. RV size and function were normal by M-mode and 2-dimensional echocardiographic criteria in 3 of the 7 donor hearts before explantation. RV enlargement or hypertrophy, or both, were present in 4 of the 7 patients.

Of the 3 patients with normal donor RV size and contractility before transplantation, 2 had progressive decrease in RV size after transplantation and had normal recipient pulmonary systolic pressures before transplantation. The third patient developed RV dilation during the initial period after transplantation, which resolved during the ensuing 4 weeks. This recipient had significant pulmonary hypertension (pulmonary artery systolic pressure 40 mm Hg) before transplantation.

In all 4 patients with donor RV dilation or hypertrophy, or both, before transplantation, donor RV size decreased by the fourth week after surgery. The 2 patients with donor RV hypertrophy before transplantation developed RV dilation during the initial period after transplantation, which subsequently resolved. Both patients had elevated pulmonary vascular resistance and pulmonary artery pressures coincident with early RV dilation after surgery.

TABLE III Spectrum of Infection in Domino and Non-Domino Heart Transplant Recipients

Infection	Events/100 Patient Days	
	Domino Patients (n = 7)	Conventional Transplant Patients (n = 80)
Bacterial	0.0859	0.1069
Fungal	0.0430	0.0292
Viral	0.2578	0.1782
Protozoal	0.0430	0.0226
Nocardial	0.0430	0.0065
Overall	0.4727	0.3434

Three of the 4 patients with donor RV dilation before transplantation developed further RV enlargement during the initial period after surgery. Pulmonary vascular resistance before transplantation was >2 Wood units, and pulmonary artery systolic pressure was normal in all 3 patients. RV size remained normal throughout the period after transplantation in the remaining patient whose pulmonary vascular resistance before transplantation was <2 Wood units.

Rejection: Rejection incidence requiring treatment in the domino-donor transplant group was 0.9524 events per 100 patient days in the first 3 months after surgery, 0.7423 in the first 6 months, and 0.5394 in the first year. Incidence of rejection for a cohort of non-domino recipients at Stanford during the same follow-up period was 1.19 events per 100 patient days in the first 3 months, 0.88 in the first 6 months, and 0.58 in the first year (p = not significant).

Infection: Table III compares infection incidence for 7 domino versus 80 conventional transplant patients

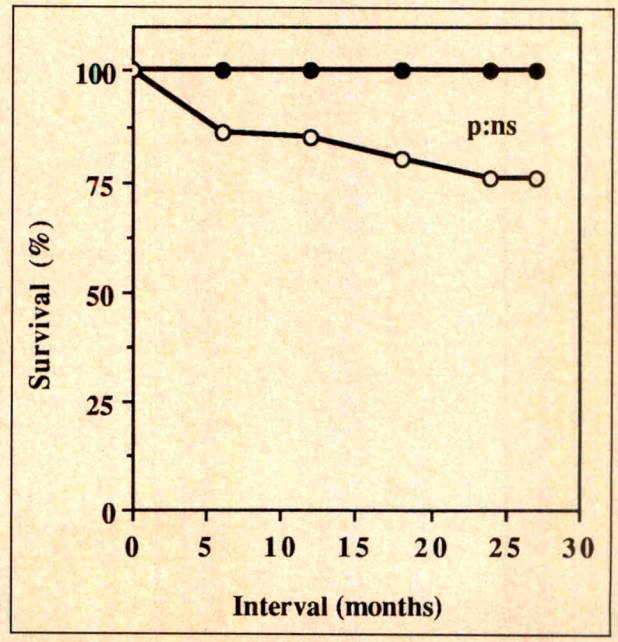


FIGURE 1. Actuarial survival in domino-donor recipients *(shaded circles)* versus that in conventional cardiac transplant recipients *(open circles)*. Actuarial survival at 1 year is 100% in 7 domino-donor recipients versus 86% in 80 conventional transplant patients. ns = not significant.

during the same period of time. Specific infections that developed in domino recipients included recurrent legionella pneumonia in 1, cytomegalovirus pneumonia in 2, and aspergillus pneumonia in 1. There was no difference in the spectrum of incidence of infections in domino-transplant patients compared with that in nondomino patients.

Other complications: Other significant complications were development of systemic hypertension in 5 patients, bradycardia needing pacemaker insertion in 2, and cholecystitis in 1.

DISCUSSION

Although the small size of this group precludes statistical analysis, our results to date with the domino-donor operation are encouraging. Potential reservations concerning domino-donor heart transplantation included the following possibilities: (1) Occult RV dysfunction unrecognized before transplantation may become overt after transplantation, with progressive RV failure and tricuspid regurgitation. (2) There may be predisposition to arrhythmias due to morphologic changes induced by the chronic high RV afterload. (3) There may be occult LV dysfunction in patients with long-standing pulmonary hypertension, because the septum is shared by both ventricles. (4) Hearts from patients with recurrent and chronic infections may possibly increase the recipients' risk of infection.

These early results indicate that patient survival after domino-donor transplantation is comparable to that of conventional orthotopic cardiac transplantation, and that there does not appear to be an increased risk of early graft failure, rejection or infection. Rejection incidence and incidence of infectious complications were similar to those of concurrent conventional cardiac transplant patients. The need for pacemakers in 2 patients may be related to some variation in surgical approach when harvesting the donor heart from a domino donor, resulting in loss of the sinus node.

Elevated pulmonary vascular resistance in cardiac recipients before surgery is correlated with predisposition to significant RV failure after surgery.[2] Hence, pulmonary vascular resistance >2.5 Wood units is considered to be a contraindication to orthotopic cardiac transplantation in most centers. A theoretical advantage of using domino donors is that the preconditioned right ventricle tolerates the increased RV afterload better than does a normal right ventricle. Previous reports have shown that in the presence of pulmonary hypertension, the normal donor right ventricle compensates by acute dilation, which is greatest 2 weeks after surgery and persists for approximately 6 weeks.[5]

In the Stanford experience with the initial 7 domino-donor heart transplants, all recipients had acceptable (≤2.5 Wood units) pulmonary vascular resistance with optimal hemodynamic manipulation before surgery, and none developed significant RV failure after transplantation. However, RV dilation early after surgery, detected by M-mode and 2-dimensional echocardiography, occurred in 4 patients. This finding was documented in nondomino cardiac transplantation and is regarded as a characteristic adaptive response of the donor right ventricle to pulmonary hypertension. Resolution of the initial RV dilation after surgery is usually seen during the subsequent 4 to 6 weeks and is thought to represent remodeling of the right ventricle. Such progressive decrease in RV cavity dimension occurred in all recipients of domino transplants irrespective of RV dilation before or early after surgery. These findings suggest that, despite exposure to chronic pulmonary hypertension, the domino donor right ventricle retained its ability for appropriate remodeling in response to decreased afterload. The ability of the right ventricle to recover both normal size and function was also described in patients after pulmonary thromboendarterectomy.[6,7]

Acute RV dilation occurred in 4 domino-donor recipients during the initial period after transplantation. In all 4 patients, evaluation before transplantation suggested an element of irreversible pulmonary vascular disease with pulmonary hypertension and existence of pulmonary vascular resistance >2 Wood units, despite optimal pharmacologic maneuvers in the catheterization laboratory. In the remaining 3 patients whose pulmonary artery systolic pressure before transplantation responded to pharmacologic agents, acute RV dilation did not occur. These findings are similar to those seen with conventional heart transplantation and provide further evidence for a normal adaptive response of the domino-donor right ventricle.

Transient episodes of LV systolic dysfunction, temporally associated with acute rejection, occurred in 2 patients. Graft failure secondary to acute rejection is well-recognized and, as in these 2 cases, will recover if antirejection therapy is promptly instituted. In the remaining 4 patients, the absence of graft failure during acute rejection episodes provides further evidence that LV function is well-preserved in the domino-donor heart and that there is no additional risk of graft failure even during rejection.

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Predictive Factors of Effectiveness of Streptokinase in Deep Venous Thrombosis

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In a prospective study, 174 patients (118 women and 56 men, average age 44 years, range 14 to 82) with proximal extensive thrombosis received streptokinase (100,000 U/hour) for an average of 2.8 days (range 0.5 to 7) through the catheter of a temporary caval filter. Twenty-seven of 45 (60%) patients with nonocclusive clots were completely free of clots at the second phlebography versus 17 of 116 (14%) with occlusive clots ($p < 0.001$). Among nonocclusive clots, proximal ones (caval, iliac and femoral) were more easily lysed than popliteal clots (88 of 116 [76%] vs 26 of 58 [45%]; $p < 0.001$). In 41 of 132 (31%) patients, a daily injection of contrast medium through the filter-carrying catheter enabled the observation of a clot in the filter, which was lysed by streptokinase. Seventy patients with follow-up >2 years (median 34 months) were examined clinically. Nineteen of 22 (86%) patients with venograms free of clots at discharge were free of clinical sequelae versus 16 of 48 (33%) without normal venograms ($p < 0.001$). It is concluded that: (1) in the case of occlusive clots, only a few patients were normalized after streptokinase; (2) proximal nonocclusive clots were most effectively lysed; (3) when venograms were free of clots at discharge, the majority of patients did not have venous sequelae at follow-up; and (4) embolic migration seems to occur frequently with streptokinase.

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The clinical sequelae of deep venous thromboses occur frequently and affect 1.5% of the population.[1] The health-care costs occasioned by their occurrence, as well as the social and professional consequences are considerable.[2] The treatment of phlebitis in the acute phase by thrombolytic therapy leads to better clot lysis than does treatment with heparin.[3] However, the former creates a greater risk of hemorrhage.[3] Various contradictory studies have been published[4–8] with respect to which kinds of clots respond best to thrombolytic therapy and with respect to the longer term benefits of early lysis. Additionally, thrombolytic treatment does not eliminate the risk of pulmonary embolism or its recurrence, and the frequency of embolic migrations has not been clearly quantified.[4,5,7–22]

The primary end point of the present study is to try to determine what type of thrombus can be lysed sufficiently to justify the added risk of hemorrhage and to try to determine the long-term clinical interest of lysis on venous sequelae. The second end point is to attempt to quantify the frequency of embolic migrations during streptokinase therapy.

METHODS

From June 1987 to January 1991 we performed a prospective study on 174 patients (118 women and 56 men, average age 44 years, range 14 to 82). Patients met the following criteria: (1) presence of demonstrated thromboembolism with symptoms over a period of <5 days; and (2) extensive thrombosis venographically documented with proximal extension above the calf veins. Exclusion criteria were any contraindications to streptokinase including: active peptic ulcer, recent history of cerebrovascular hemorrhage or ischemia, known bleeding tendency, previous allergic reaction to streptokinase, hemorrhagic proliferative or hemorrhagic diabetic retinopathy, severe systemic hypertension (systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg, or both), known pericarditis or endocarditis, pregnancy, major surgery in the past 10 days, recent puncture of a noncompressible vessel, and recent organ biopsy. We also eliminated patients with pulmonary embolism and shock, for whom it would be impossible to perform the baseline phlebography.

Before treatment, all patients underwent a bilateral ascending contrast venography. Only anterior roentgenograms were obtained. Iliocavography was performed if the visualization of these veins was of poor quality. Of 174 patients studied, 113 (65%) had clinical pulmonary embolism; all but 1 underwent pulmonary angiography.

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Sixty-one patients had no clinical pulmonary embolism and underwent only a lung scan (ventilation perfusion). In the presence of an inconclusive lung scan, absence of pulmonary embolism was confirmed by angiography. When proximal deep venous thrombosis was noted, a temporary caval filter was introduced according to a technique previously described.[23,24] Briefly, the filter (PROTHIA, Montrouge, France) consists of a small diameter catheter (7Fr) introduced by a venous percutaneous puncture. A side port permits the infusion of liquids. The catheter contains a filter that can be opened by advancing the proximal rigid section of an internal wire. The position of the filter was checked by fluoroscopy, and it was opened in the inferior vena cava. We were able to position the filter satisfactorily in 173 of 174 attempts; in 1 case, a cardiac perforation forced us to interrupt the procedure. In the first 128 patients, the device was introduced through a jugular (n = 33) or femoral (n = 95) approach. For the 46 subsequent patients, a minor modification in the device allowed us to introduce the filter through the brachial vein. When the filter was positioned, the injection of a few milliliters of contrast medium using digital angiography was performed to verify that the filter was free of clots. Each day we injected a few milliliters of contrast medium into the catheter to check the permeability of the filter. After use, the filter was drawn into the catheter by pulling the proximal wire, and the entire system was removed. Immediately after positioning of the filter, streptokinase was infused by the lateral arm of the catheter at a dosage of 100,000 U/hour without a loading dose. The average duration of treatment was 2.8 days (range 0.5 to 7). At termination of streptokinase treatment, patients underwent another venography, as well as a pulmonary angiography or lung scan, and the filter was removed. Of 173 patients, 12 underwent neither a control venocavography nor a lung scan (5 deaths, 3 early dismissals, 2 refusals and 2 for technical reasons). In all, 161 patients underwent the entire protocol, and the results were analyzed. Heparin was initiated 4 hours after the cessation of streptokinase, and its dosage was adjusted to keep the activated partial thromboplastin time between 2.5 and 3 times the control. After heparin, fluindione was administered for 6 months. The daily dosage of fluindione was adjusted for an international normalized ratio of 2 to 4.

The venograms, angiograms and lung scans were subsequently reviewed by an independent panel of 3 radiologists. A thrombus was defined as nonocclusive when the clot was outlined by contrast on an anterior roentgenogram. A thrombus was defined as occlusive when the vein was not opacified by contrast medium. At the second phlebography we considered the lysis completed when no thrombus remained, and partial if ≥50% of the thrombus had been lysed; failure was defined as lysis <50%, including the absence of lysis, and aggravation of the obstruction. Phlebographies were examined in segments (1 segment for the vena cava, 1 for the iliac veins, 1 for the femoral veins, and 1 for the popliteal veins). Seven segments were studied in each patient.

Follow-up: We limited the follow-up portion of our study to 98 patients treated >2 years before follow-up. We used the severity score developed by Kakkar and Lawrence (absence of symptoms and signs: 0; minor aches or pains, or minimal edema: 1; moderate pain, aching, venular "flare" or marked edema: 2; chronic pain, aching, induration and pigmentation: 3; and frank ulceration: 4).[25] The maximal score possible was 10 points. Only 98 patients with follow-up >2 years were retained for consideration in the follow-up study. Nineteen (20%) of these patients were lost to follow-up (11 changed address and 8 refused to participate). Nine of the remaining 79 patients died (4 cancer, 1 myocardial infarction and 4 unidentified causes). In all, 70 patients were examined, and mean delay of follow-up was 34 months (range 25 to 45).

Statistical analysis: Differences in categorical variables were assessed by chi-square analysis. Differences were considered to be significant when the p value was <0.05.

RESULTS

In 161 patients studied, 455 segments were thrombotic on initial phlebography. Nonocclusive clots were lysed more easily than occlusive ones were, and better results were obtained with nonocclusive proximal (vena caval, iliac and femoral) than with popliteal clots. When clots were occlusive, their localization did not reveal itself to be a significant factor (Table I).

We also studied individual patient progress by phlebography. Patients with both a nonocclusive and occlusive clot were considered in the occlusive group. Thirty-five of 45 (78%) patients with nonocclusive thrombi improved (complete or partial lysis) compared with only 39 of 116 (34%) with occlusive thrombi. Complete lysis was observed in 27 of 45 (60%) patients with nonocclusive thrombi compared with 17 of 116 (14%) with occlusive thrombi ($p < 0.001$).

Filter permeability: Examination of filter permeability was possible in 132 patients. In 21 of 63 (33%) cases with nonocclusive clots and in 20 of 69 (29%) with occlusive clots, a thrombus was detected in the filter on examination the day after initiation of thrombolytic therapy. Repeated controls each day thereafter revealed progressive lysis of the thrombus. In 31 of 41 (76%) cases, the clots were <10 mm and in 10 (24%) they were larger (the largest measured 6.5 cm in length, and 2 cm in width on an anterior view). In 8 of 21 cases of nonocclusive clots, the appearance of a clot in the filter corresponded to the disappearance of a more distal venous clot (Figure 1). In all cases we were able to collapse and remove the filter. No sign of recurrent pulmonary embolism was detected in the lung scans or angiograms after removal of the filter.

Side effects: Five mortalities occurred during hospitalization. A 58-year-old man had a myocardial infarction on the third day. A 67-year-old woman with a tachyarrhythmia had a stroke on the third day of streptokinase treatment. Scans performed on days 3 and 5 revealed zones of cerebral ischemia without hemorrhage, and the woman died on day 6. A 58-year-old

TABLE I Phlebographic Results Obtained in Venous Segments at Discharge

		Nonocclusive Clots	Occlusive Clots
Caval (n = 46)		n = 36	n = 10
	Complete lysis	30 (83%)	0 (0%)
	Partial lysis	3 (8%)	3 (30%)
	Failure	3 (8%)	7 (70%)
Iliac (n = 112)		n = 24	n = 88
	Complete lysis	21 (87%)	18 (20%)
	Partial lysis	1 (4%)	10 (11%)
	Failure	2 (8%)	60 (68%)
Femoral (n = 154)		n = 56	n = 98
	Complete lysis	37 (66%)	20 (20%)
	Partial lysis	5 (9%)	4 (4%)
	Failure	14 (25%)	74 (75%)
Proximal clots (caval + iliac + femoral) (n = 312)		n = 116	n = 196
	Complete lysis	88 (76%)	38 (19%)
	Partial lysis	9 (8%)	17 (9%)
	Failure	19 (16%)	141 (72%)
		$p < 0.001$	NS
Popliteal (n = 143)		n = 58	n = 85
	Complete lysis	26 (45%)	19 (22%)
	Partial lysis	7 (12%)	1 (1%)
	Failure	25 (43%)	65 (77%)
All segments (n = 455)		n = 174	n = 281
		$p < 0.001$	
	Complete lysis	114 (66%)	57 (20%)
	Partial lysis	16 (9%)	18 (6%)
	Failure	44 (25%)	206 (73%)

NS = not significant.

patient died of cerebral hemorrhage 10 hours after the initiation of thrombolytic therapy. A 77-year-old woman with a pulmonary embolism estimated at 50% according to the Miller index[26] had pneumonia and needed intubation, respiratory assistance and antibiotic treatment; she died on day 6. A 72-year-old woman died from a recurrence of pulmonary embolism 8 days after removal of the filter while under vitamin K-antagonists. The remaining 169 patients were discharged after an average of 7.8 days (range 3 to 23). In 1 patient, cardiac perforation without tamponade occurred during positioning of the filter before initiation of streptokinase therapy. The outcome was favorable.

Major bleeding (defined as cerebral hemorrhage, transfusions of >2 units of blood, or loss of >5 g of hemoglobin) was observed in 26 of 173 cases (15%). Major bleeding occurred more frequently in the first patients treated (filter introduced by a jugular or a femoral approach; 26 of 128 [18.7%]) than in the subsequent ones (2 of 46 [4.3%]); brachial introduction used for the latter patients resulted in a significant reduction in hematomas ($p = 0.001$). Bleeding resulted in 1 death (the case of cerebral hemorrhage mentioned previously). In all other cases, these complications did not induce sequelae. There were 10 hematomas at the site of the puncture (4 at the psoas, 6 metrorrhagia and 5 melena). Furthermore, 110 patients developed a pyrogenic reaction (>38°C) at the outset of thrombolytic therapy; fever subsided at the cessation of streptokinase administration.

Follow-up: Of the 70 patients examined, 22 had complete relief of the obstruction at the time of discharge, 40 had unsuccessful treatment and 8 had a partial lysis. Of patients discharged with a complete lysis, 19 (86%) were in clinical class 0 or 1 compared with 16 of 48 (33%) with unsuccessful treatment or partial lysis ($p < 0.001$).

DISCUSSION

Deep venous thromboses, especially those that are proximal,[16] are responsible for postthrombotic syndrome, which can produce severe clinical sequelae with a socioeconomic impact.[2] Thrombolytic therapy is more effective than heparin in the lysis of clots in the lower limbs,[3,27] but the risk of hemorrhage is greater.[3] This risk renders valuable the determination of which types of thrombi are best suited to thrombolytic therapy. Several studies reported that proximal clots are more easily lysed than are distal clots.[19,28,29] This finding was challenged by Arnesen et al.[7] Furthermore, it was reported that nonocclusive clots were more readily lysed,[4–6,8] but again other studies have yielded contradictory results.[7]

Our results show significantly better lysis in cases of nonocclusive than of occlusive thrombi. Only 14% of patients with occlusive thrombosis were discharged with complete lysis compared with 60% of those with nonocclusive thrombosis. Of nonocclusive clots, popliteal clots are more difficult to lyse than more proximal ones are. The relation between the immediate phlebographic and long-term clinical results is a matter of some controversy. According to Kakkar and Lawrence,[25] although lysis is greater with thrombolytic therapy than with heparin, long-term (24 months) venous sequelae are not less frequent. Other studies[4,8,30,31] came to the opposite conclu-

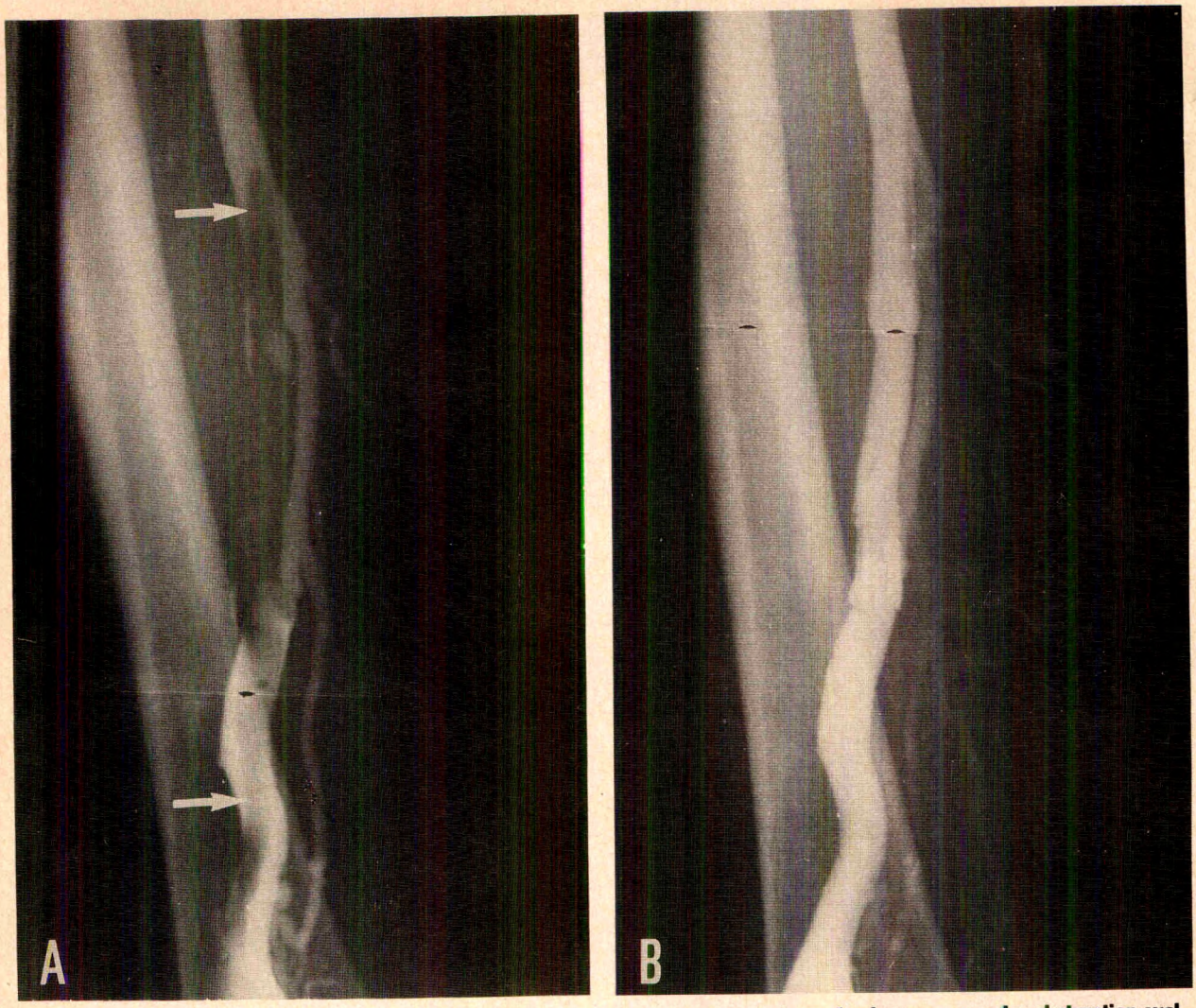
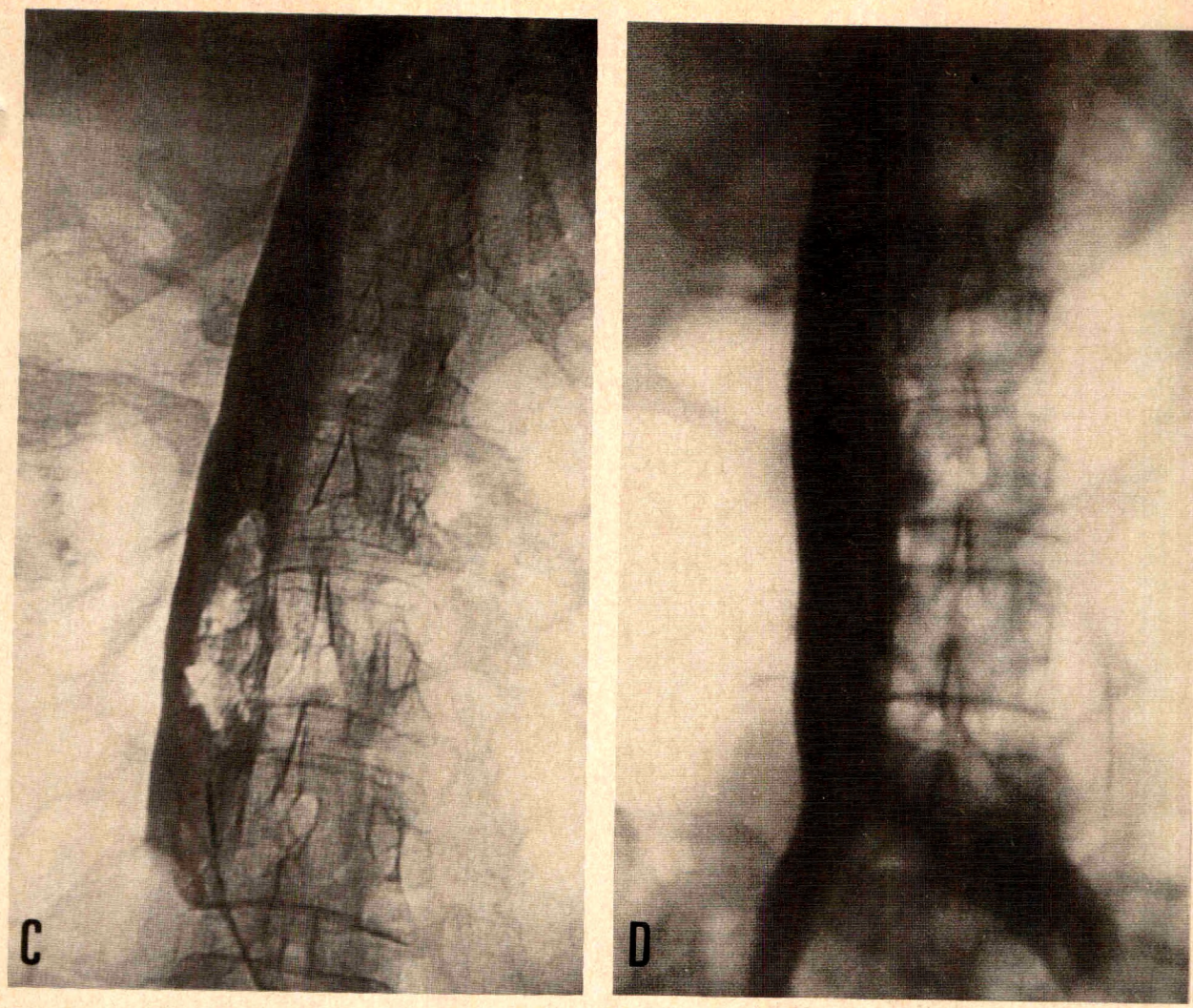


FIGURE 1. Sixty-seven-year-old woman with massive pulmonary embolism (percentage of pulmonary vascular obstruction evaluated at 75%). Phlebography revealed femoropopliteal clot 17 cm long *(arrows) (A)*. Patient received treatment combining streptokinase and temporary vena caval filter. Phlebography performed 24 hours later showed disappearance of thrombus *(B)*.

sion. In our study, 86% of patients with normal phlebograms at discharge had no or very mild clinical sequelae after an average follow-up of 34 months; however, 67% of those with residual venous occlusion at discharge had sequelae. Good short- and long-term results obtained in nonocclusive proximal occlusions argue in favor of use of streptokinase on such thromboses. However, the small chance of success in occlusive clots could limit indications owing to the risk of hemorrhage produced by the therapy.

Another problem posed by the use of thrombolytics is embolic migration. Streptokinase may lyse a clot in situ, but there is a risk of fragmentation leading to pulmonary embolism or its recurrence. In the Urokinase-Pulmonary Embolism Trial,[32] with urokinase, recurrence occurred in 17% of patients and was responsible for a 1.2% mortality rate. With streptokinase, this phenomenon was not reported in some studies,[4,5,9–16] whereas in others it was frequently observed.[7,8,17–22] The frequency of recurrence varies depending on whether the diagnosis of pulmonary embolism is based on clinical examination, CAT scan or pulmonary angiography. Angiography and scanning are more sensitive than clinical examination, but do not distinguish between true recurrence and mobilization of a saddle embolus. We tried to calculate the frequency of recurrence by performing a radiologic control of the temporary filter during thrombolysis. We noted that in approximately 30% of the patients, a thrombus appeared in the filter. Two mechanisms could explain the presence of the clot in the filter: an in situ thrombosis or the blockage of a fragmented, detached clot. The more likely hypothesis is that of a detached fragment, because we imaged the filter after positioning it to check that it was free of any obstruction; furthermore, clots that were observed in the filter, later disappeared. Furthermore, in 8 cases the appearance of a thrombus in the filter corresponded to the disappearance of an underlying nonocclusive clot. The disappearance of the thrombus was caused by streptokinase and not by a pulmonary embolic migration, because scanning or angiography performed after therapy never showed any sign of a recurrence of pulmonary



Cavography made possible by injecting a few milliliters of contrast medium through the filter-carrying catheter and by digital angiography (performed simultaneously) revealed thrombus in filter *(C)*. Thrombus disappeared. Filter was removed. Cavography was normal 48 hours later *(D)*.

embolism. If one accepts the hypothesis of the filter's entrapping embolic migrations, the phenomenon appears to occur frequently. In 76% of the cases studied, the entrapped thrombi were so small that their clinical significance probably would have been slight; however, in 24% the clots were large and would have probably been dangerous had they been allowed to reach the pulmonary vessels already severely affected.

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Cardiovascular Factors Influencing Survival in End-Stage Renal Disease Treated by Continuous Ambulatory Peritoneal Dialysis

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To determine whether hemodynamic advantages of continuous ambulatory peritoneal dialysis (CAPD) over intermittent hemodialysis are associated with improved survival and identify cardiac risk factors for early death, 55 patients on CAPD (age 58 ± 11 years; CAPD duration: 29 ± 25 months) were followed in a noninvasive prospective analysis over 35 months. At follow-up, 25 patients had died; 16 deaths were related to cardiovascular causes. Nonsurvivors were older (62 ± 8 vs 55 ± 12 years; p <0.015) and had more angina pectoris (40 vs 20%; p <0.05) than survivors, but had comparable CAPD duration, arterial blood pressure, hemoglobin, serum creatinine, urea and parathyroid hormone concentrations. On echocardiography, nonsurvivors had a lower mean left ventricular (LV) ejection fraction (59 ± 15 vs 66 ± 9%; p <0.03), higher LV end-systolic volume indexes (49 ± 31 vs 36 ± 13 ml/m^2; p <0.03) and a shorter mean LV ejection time (371 ± 41 vs 390 ± 22 ms; p <0.03). LV muscle mass, LV diastolic and left atrial dimensions, stroke volume and cardiac index were comparable. On pulsed Doppler analysis of a subgroup of 48 patients in sinus rhythm and without valve disease, nonsurvivors (n = 23) had more severely decreased ratios of peak early/atrial filling velocities (0.66 ± 0.18 vs 0.81 ± 0.24; p <0.03) and increased atrial filling fractions (52 ± 11 vs 46 ± 9%; p <0.03) than survivors. Mean isovolumic relaxation periods were increased in both groups (135 ± 39 vs 129 ± 33 ms; p >0.05). These data suggest that older age, and reduced LV systolic and diastolic functions are attributed to increased mortality in patients with CAPD, whereas a significant influence of LV muscle mass and CAPD duration is not.

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Life expectation of patients with end-stage renal disease is greatly reduced because of cardiovascular complications.[1] Increased cardiovascular mortality is associated with left ventricular (LV) hypertrophy in patients on intermittent hemodialysis.[2,3] Although this has also been suggested a mortality risk factor for patients on continuous ambulatory peritoneal dialysis (CAPD) treatment,[4,5] no information exists on the influence of systolic, and especially diastolic, LV dysfunction on long-term mortality. Because the clinical relevance of these factors is suggested from data on short-term survival during surgical intervention,[6] we studied their influence on long-term survival over 35 months in 55 patients on CAPD with echocardiography and Doppler echocardiography. Data of survivors and nonsurvivors are compared.

METHODS

Patients: In the echocardiographic study, 55 consecutive CAPD outpatients who returned for a routine, scheduled consultation were analyzed. A subgroup of 48 patients with sinus rhythm and without significant valvular disease on color flow Doppler was included in the pulsed wave Doppler analysis. At the end point of the study after 35 months, 25 patients in the initial group had died. In 16 patients, death could be directly related to clinically relevant cardiac events; in most of the remaining 9 patients, symptoms of heart failure or vascular problems preceded complications such as pulmonary embolism, pneumonia or abdominal infarction. Of 30 patients who were alive at follow-up, 16 had remained on CAPD, 3 had undergone transplantation and 3 had changed to hemodialysis treatment. Blood pressure values are presented as average measurements from the last 2 weeks before the examination. Blood chemistry was analyzed before the instillation of intraperitoneal dialysis solution.

Echocardiography: Echocardiographic determinations were obtained with the patient in the left lateral recumbent position after a 15-minute rest period and with no intraperitoneal dialysis solution installed. Echocardiography was performed with a Hewlett Packard 77 020A echo and Doppler system. A 2.5 MHz transducer was selected for 2-dimensional and M-mode echocardiograms from parasternal and apical windows. Echocardiograms were recored on a Panasonic 6300 VCR and evaluated according to the standards of the American Society of Echocardiography,[7] using average values of 5 consecutive cardiac cycles. LV volumes and masses were calculated from the apical 4-chamber view using standard formulas. For the purpose of this study,

TABLE I Clinical Characteristics of 35 Survivors and 25 Nonsurvivors of CAPD Therapy After 35 Months of Follow-Up

	Survivors		Nonsurvivors
No. of patients	30 —		25 —
Angina pectoris (%)	20 —	*	40 —
CAPD duration (mos)	29 ± 28		29 ± 21
Weight (kg)	68 ± 12		65 ± 13
Body surface area (m^2)	1.78 ± 0.2		1.65 ± 0.4
Systolic arterial BP (mm Hg)	138 ± 19		134 ± 19
Diastolic arterial BP (mm Hg)	80 ± 10		76 ± 11
Cardiovascular drugs	1.8 ± 1.1		1.6 ± 1.2
Age (years)	55 ± 12	†	62 ± 8
Hemoglobin (g/dl)	9.7 ± 1.7		9.7 ± 1.9
Urea (mg/dl)	63 ± 20		63 ± 14
Creatinine (mg/dl)	9.6 ± 3.6		10.1 ± 2.3
Parathyroid hormone (pg/liter)	1,211 ± 560		1,079 ± 501

*$p < 0.05$; †$p < 0.015$.
Values are expressed as mean ± standard deviation.
BP = blood pressure; CAPD = continuous ambulatory peritoneal dialysis.

TABLE II Echocardiographic Parameters of Left Ventricular Systolic Function of 35 Survivors and 25 Nonsurvivors of CAPD Therapy

	Survivors		Nonsurvivors
Heart rate (beats/min)	80 ± 12		80 ± 12
LV end-diastolic diameter (mm)	51.9 ± 6		52.9 ± 7
LV end-systolic diameter (mm)	30.7 ± 6		34.4 ± 10
Left atrial diameter (mm)	41 ± 7		42 ± 8
LV end-diastolic volume index (ml/m^2)	103 ± 22		112 ± 35
LV end-systolic volume index (ml/m^2)	36 ± 13	*	49 ± 31
LV ejection fraction (%)	66 ± 9	*	59 ± 15
VCF (circ/s)	1.65 ± 0.4	*	1.56 ± 0.5
Cardiac index ($liters/min/m^2$)	5.4 ± 1.3		4.9 ± 1.3
LV muscle mass (g)	270 ± 75		294 ± 99
LV muscle mass index (g/m^2)	151 ± 37		170 ± 59
LV volume/mass ratio (ml/g)	0.7 ± 0.2		0.7 ± 0.2
Preejection period (ms)	151 ± 20		149 ± 19
LV ejection time (ms)	390 ± 22	*	371 ± 41
PEP/LVET	0.39 ± 0.01		0.4 ± 0.01

*$p < 0.03$.
Values are expressed as mean ± standard deviation.
CAPD = continuous ambulatory peritoneal dialysis; circ = circumference; LV = left ventricular; PEP/LVET = preejection period/left ventricular ejection time ratio; VCF = velocity of circumferential fiber shortening.

the following conventions were made: (1) normal LV wall thickness, end-diastolic <12 mm; moderate (severe) LV hypertrophy, end-diastolic 12 to 14 mm (>14 mm); (2) normal LV end-diastolic diameter, LV end-diastolic diameter <56 mm; moderate (severe) LV dilatation, LV end-diastolic diameter 56 to 60 mm (>60 mm); and (3) normal LV ejection fraction, LV ejection fraction >55%; moderate (severe) systolic dysfunction, LV ejection fraction 40 to 55% (<40%).

Pulsed Doppler echocardiography: Pulsed Doppler examinations of the LV inflow tract were performed under 2-dimensional guidance from the apical 4-chamber view. The sample volume was positioned at the tips of the mitral valve leaflets and aligned so that the angle between the ultrasound beam and the blood flow vector as determined from the color flow image was as close to zero as possible. An average of 5 consecutive cycles was taken from the following measurements: (1) peak velocity of early and late LV filling (peak E, peak A) and their ratios[8–10]; (2) early and atrial time velocity integrals and their ratios including atrial filling fraction[8]; and (3) peak filling velocity normalized for mitral stroke volume.[11] A ratio of peak early/atrial filling velocities (E/A max) was considered normal for values of >1 for the age group of the study population.[8,12–14] For the purpose of this study, moderate (severe) LV diastolic dysfunction was defined as a ratio of E/A max 0.8 to 1 (<0.8).

Statistics: Data are reported as mean ± standard deviation. Student's *t* test for paired data was used to determine the significance of differences. A correlation coefficient was considered significant for a probability of error at $p < 0.05$.

RESULTS

Clinical characteristics and blood chemistry: Clinical data are summarized in Table I. The investigation covers a wide range of patient age (31 to 76 years at onset) and CAPD duration (5 to 96 months at onset). Despite extensive antihypertensive medication, 5 patients presented with borderline hypertension (140 to 160 mm Hg systolic). Clinical angina pectoris did not occur as often in survivors (20% of patients) as in nonsurvivors (40% of patients). Nonsurvivors were significantly older than survivors, but had comparable total CAPD duration, body weight, blood pressure and average number of cardiovascular drugs. Also, mean hemoglobin concentration, parameters of blood purification and parathyroid hormone concentrations were comparable in both groups. Major causes of death were cardiovascular problems (64%) and infections (16%). Two patients died of carcinoma (breast and gastric), one patient died of pulmonary embolism and 1 of ileus after an abdominal infarction and pancreatitis.

Echocardiographic parameters: On echocardiography, parameters of LV systolic performance in survivors were better over those of nonsurvivors (Table II): in survivors, mean LV ejection fraction, velocity of circumferential fiber shortening, and LV ejection time were greater, and mean LV end-systolic volume was smaller than in nonsurvivors ($p < 0.03$). Individual data of end-systolic volume index and ejection fraction are depicted in Figure 1. Mean LV muscle mass index and left atrial diameter tended to be smaller in survivors, but this difference did not reach significance. Average heart rate, cardiac index, LV end-diastolic diameters, volume and volume/mass ratios were comparable.

Doppler echocardiographic parameters: On Doppler analysis (Table III), LV diastolic dysfunction was greater in nonsurvivors than in survivors: Mean ratios of peak early/atrial filling velocities were smaller and atrial filling fractions were greater in nonsurvivors than in survivors (Figure 2). Isovolumic relaxation time was comparably prolonged in both groups. No significant difference was observed in heart rate, peak filling rate normalized for mitral stroke volume, and time-velocity integrals of early and atrial filling waves.

Prevalence of echocardiographic and Doppler echocardiographic abnormalities: Echocardiographic and Doppler echocardiographic abnormalities by order of severity are depicted in Figure 3. Although the preva-

lence of LV hypertrophy and dilatation was comparable among survivors and nonsurvivors, more nonsurvivors had reduced LV ejection fraction and reduced peak early/atrial filling velocity ratios than survivors.

DISCUSSION

Although LV systolic function is superior in patients on CAPD compared with patients on intermittent hemodialysis,[15] the presented data identify severe LV dysfunction and older age as major determinants of survival in patients on CAPD.

Left ventricular hypertrophy and function: Abnormalities of LV diastolic function often precede the development of LV hypertrophy, whereas LV systolic dysfunction may precede cardiac decompensation at a late stage of the disease. In end-stage renal disease, fluid overload (increased preload) and arterial hypertension (increased afterload) often contribute to a combination of eccentric and concentric LV hypertrophy, which may be influenced both by adequate volume and pressure control.[16–19] Whereas moderate LV diastolic dysfunction may persist even after regression of LV hypertrophy because interstitial fiber content remains increased, severe LV diastolic and systolic dysfunctions appear to be associated with cardiac decompensation and indicate poor prognosis.

Previous echocardiographic investigations on dialysis patients identified the amount of LV hypertrophy as a factor crucial for survival: Silberberg et al,[4] following 91 patients over a mean of 19 months, found a relative risk for cardiac mortality of 3.7 in patients with LV

TABLE III Doppler Echocardiographic Parameters of Left Ventricular Diastolic Filling of 25 Survivors Compared with Data of 23 Nonsurvivors Including Only Patients on CAPD in Sinus Rhythm and Without Significant Valve Disease*

	Survivors		Nonsurvivors
Heart rate (beats/min)	79 ± 12		80 ± 13
Peak early flow velocity (cm/s)	69 ± 23		65 ± 24
Peak atrial flow velocity (cm/s)	88 ± 25		99 ± 24
Early/late peak flow velocities	0.81 ± 0.24	†	0.66 ± 0.18
Early diastolic time-velocity integral (cm)	9.7 ± 4.5		8.8 ± 4.3
Late diastolic time-velocity integral (cm)	7.7 ± 2.8		9 ± 2.7
Atrial filling fraction (%)	46 ± 9	†	52 ± 11
Normalized peak filling rate (liters/s)	7.7 ± 1.8		8.4 ± 2.9
Isovolumic relaxation period (ms)	129 ± 33		135 ± 39

*Mean ratio of peak early/atrial flow velocities is severely decreased in nonsurvivors; mean atrial filling fraction is higher in nonsurvivors than in survivors.
†$p < 0.03$.
CAPD = continuous ambulatory peritoneal dialysis.

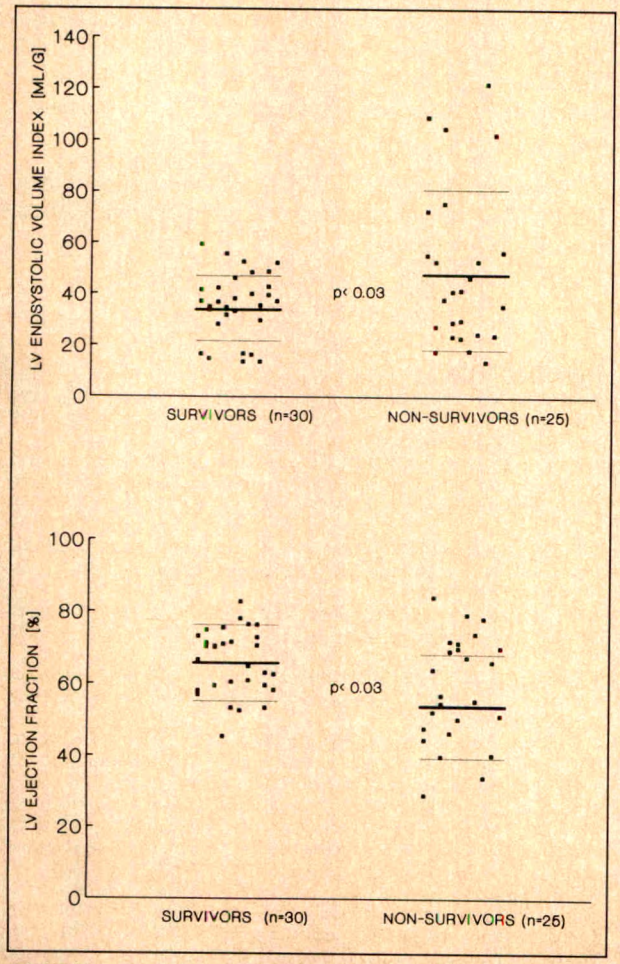


FIGURE 1. Parameters of left ventricular (LV) systolic function were significantly different in survivors versus nonsurvivors.

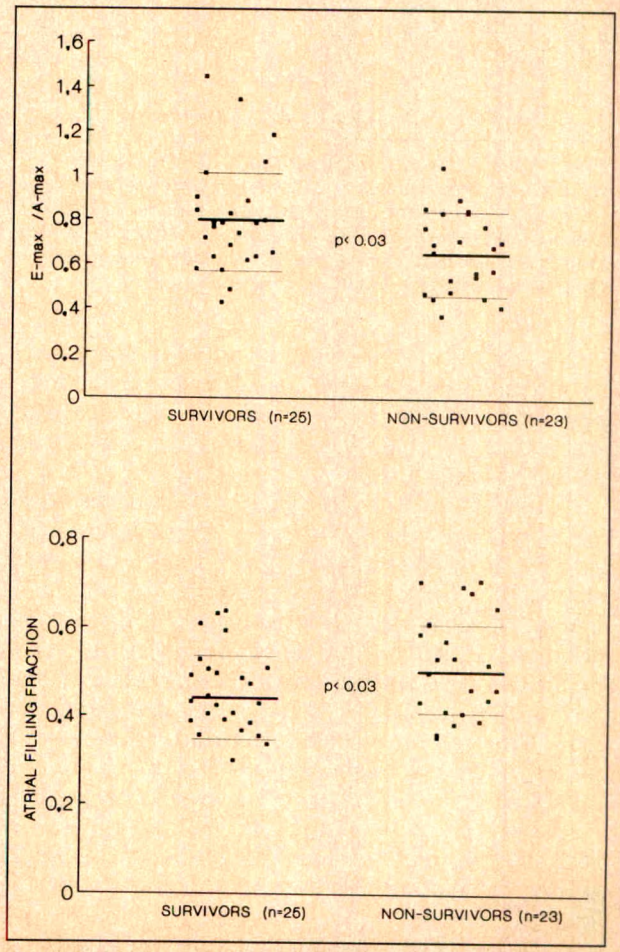


FIGURE 2. Left ventricular diastolic filling was more severely impaired in nonsurvivors than in survivors. The mean ratio of peak early/atrial filling velocities (E-max/A-max) decreased, and mean atrial filling fraction increased in nonsurvivors compared with survivors.

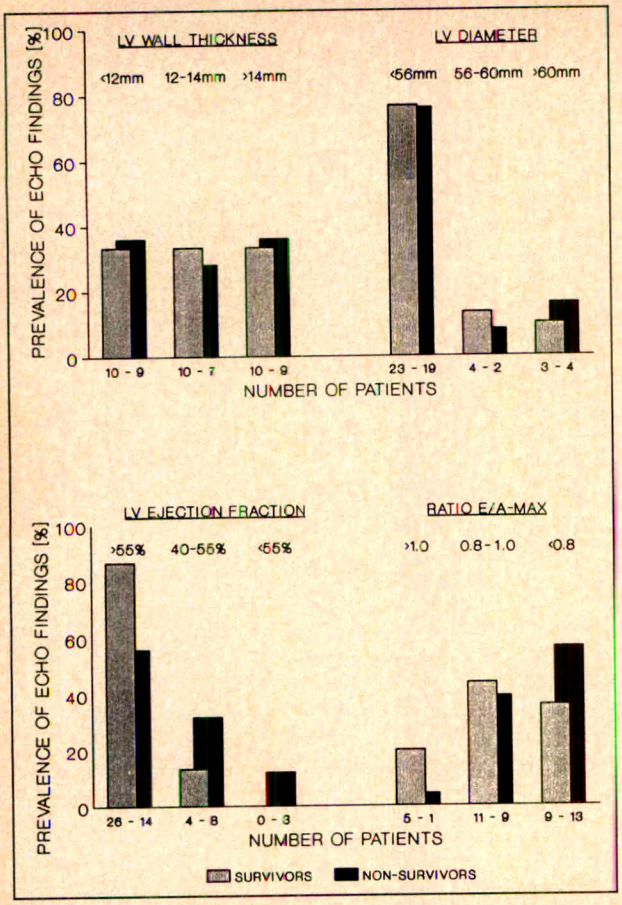


FIGURE 3. Prevalence of left ventricular (LV) hypertrophy and dilatation was comparable in survivors versus nonsurvivors; number of patients with moderately reduced LV systolic function and severely impaired LV diastolic filling was greater in nonsurvivors than in survivors. E/A-MAX = peak early/atrial filling velocities; ECHO = echocardiographic.

hypertrophy. As in our study, the risk of cardiac mortality increased (by 3.8 times) as LV end-systolic dimensions increased and (by 15 times) with older age. Also, the relative risk of cardiac death for patients with angina increased (by 9.2 times).

Although nonsurvivors tended to have more severe LV hypertrophy than survivors, this was not a significant factor in our study. However, almost all patients described by Silberberg et al[4] were treated with intermittent hemodialysis. The importance of severe LV hypertrophy for survival in their study may be explained by the fact that acute changes of intravascular volume such as those that occur in patients on intermittent hemodialysis may often cause hypotension because of insufficient filling pressure, impaired LV compliance[20,21] and atrial arrhythmia.[22] Our data lead us to conclude that severe LV diastolic dysfunction is relevant for survival not only in patients on dialysis who undergo rapid volume changes, but also in those with constant volume control.

Left ventricular hypertrophy and survival: In a group of 27 patients on CAPD followed for a minimum of 6 months, Eisenberg et al[5] found mortality to be highest (56%) in patients with severe LV hypertrophy and to be increased (25%) in those with mild hypertrophy. None of the patients with normal LV muscle mass died. LV end-systolic diameters were higher in patients with a poor outcome than in those with good prognosis comparable to data from our study.

Left ventricular diastolic function and survival: Our data are in agreement with results of Himelman et al,[6] who emphasized the prognostic relevance of impaired LV diastolic filling on Doppler analysis: In a study on the clinical outcome of 41 patients on hemodialysis during the perioperative transplant period, 13 of 19 patients with altered diastolic LV function developed perioperative pulmonary edema compared with only 1 of 9 patients with normal LV diastolic filling.

Study limitations: It is an obvious limitation of our study that no autopsy data can be presented: Although it is one of the major advantages of CAPD that patients are independent from the treating dialysis center, this was a drawback for the analysis of data. Frequently, patients died at home or at other institutions, and death was often reported too late to allow autopsy. Because we are not certain that the clinically determined cause of death is correct in all cases, we did not form subgroups related to cardiac versus noncardiac cause of death, but used death as the uniform end point of the study for all patients.

Clinical relevance of findings: The present analysis identifies severe diastolic and moderate systolic LV dysfunction as predictors of death in patients on CAPD. Therefore, elderly patients on CAPD with these risk factors deserve special attention from the cardiologist's standpoint.

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Left Ventricular Function in Myasthenia Gravis

Karl-Arne Johannessen, MD, Åse Mygland, MD, Nils Erik Gilhus, MD, Johan Aarli, MD, and Harald Vik-Mo, MD

Myasthenia gravis is an autoimmune disorder with autoantibodies to acetylcholine receptors of skeletal muscle. Left ventricular diastolic function was studied with M-mode and Doppler echocardiography in 25 patients with myasthenia and in a group of age- and heart rate-matched control subjects. In the patients, diastolic peak filling rate was reduced by 37%, and Doppler peak early filling velocity (E) was reduced by 12% compared with the control subjects (2.7 ± 0.7 vs 4.2 ± 1.0 s^{-1}, and 76 ± 8 vs 85 ± 15 cm/s, respectively; p <0.05). Peak atrial filling velocity (A) was increased by 38% (68 ± 17 vs 48 ± 9 cm/s; p <0.01), and consequently the E:A ratio in the group of patients was reduced by 33% (1.22 ± 0.40 vs 1.81 ± 0.33; p <0.001). End-diastolic dimension was 5.0 ± 0.5 cm in both groups, heart rate was 70 ± 12 vs 68 ± 16 beats/min (p = not significant [NS]), M-mode ejection fraction was 76 ± 8 vs 79 ± 5% (p = NS), M-mode peak ejection rate was −1.9 ± 0.4 vs −2.1 ± 0.3 s^{-1} (p = NS), and peak aortic outflow velocity was 109 ± 18 vs 98 ± 13 cm/s (p = NS). Twenty-three patients and 15 control subjects were studied before and after intake of the acetylcholine-esterase inhibitor pyridostigmine. Whereas diastolic measures were unaltered in the control group, peak filling rate in the patients increased by 23% (2.7 ± 0.7 to 3.3 ± 0.9 s^{-1}; p <0.01), E increased by 9% (76 ± 14 to 83 ± 15 cm/s; p <0.05), A decreased by 9% (68 ± 17 to 62 ± 17 cm/s; p <0.01) and the E:A ratio increased by 16% (1.22 ± 0.4 to 1.42 ± 0.4; p <0.01). Heart rate and systolic measures were unaltered in both groups after pyridostigmine. It is concluded that diastolic filling is impaired in some patients with myasthenia gravis and that pyridostigmine tends to normalize the diastolic function in these patients.

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Myasthenia gravis is an autoimmune disorder with autoantibodies to nicotinic acetylcholine receptors of skeletal muscle. The clinical symptoms are caused by antibody-binding to these receptors at the neuromuscular junction. Despite several reports of cardiac involvement in myasthenia, including giant cell and granulomatous myocarditis,[1–4] previous studies of left ventricular (LV) systolic function have not reported abnormal cardiac findings. Several cholinergic responses are of importance in the regulation of cardiac performance and thus may influence cardiac function in patients with myasthenia.[5–8] These include atrial inhibition mediated by muscarinic receptor stimulation, and increased inotropy mediated by nicotinic receptor stimulation. Acetylcholine-esterase inhibitors relieve the muscular symptoms in patients with myasthenia by increasing the levels of acetylcholine.[9,10] The effects of these drugs on cardiac function are unknown.

M-mode and Doppler echocardiography may be used to study systolic[11–13] and diastolic[14–16] LV functions. Diastolic measures are closely correlated to age and heart rate,[17–19] and these factors must therefore be taken into consideration in cross-sectional studies of patients with varying ages and heart rates. The objectives of the current study were to examine whether LV diastolic function is altered in myasthenia gravis and whether the acetylcholine-esterase–inhibiting drug pyridostigmine influences cardiac function assessed by echocardiography.

METHODS

Study subjects: Twenty-five consecutive patients (aged 44 ± 14 years, range 21 to 74) with myasthenia gravis were examined in a prospective study. The diagnosis was based on conventional clinical criteria, positive edrophonium test, increased decrement after repetitive motor nerve stimulation, increased jitter on single-fiber electromyography, and increased acetylcholine receptor antibody concentration. Patients with cardiovascular disease, hypertension, diabetes mellitus or pulmonary disease were excluded from the study. An age- and heart rate-matched group of 25 volunteers (aged 44 ± 16 years, range 22 to 82) served as control subjects. No control subjects had history or signs of cardiovascular disease, and all had a normal electrocardiogram at rest and Doppler echocardiographic study.

M-mode and Doppler echocardiography: All subjects were studied in the morning after a light meal. No subjects were receiving any drugs with known cardiovascular effects, and the patients did not receive any anticholinesterase medication for ≥10 hours before the study. The subjects were placed in the left lateral position and were not moved until the final Doppler echocardiographic registration had been obtained. After

TABLE I Diastolic Measures in 25 Patients with Myasthenia Gravis and in 25 Control Subjects

	Myasthenia Gravis (n = 25)	Control Subjects (n = 25)	p Value
Diastolic filling period (ms)	500 ± 108	490 ± 90	NS
Isovolumic relaxation time (ms)	86 ± 13	90 ± 15	NS
M-mode peak filling rate (s^{-1})	2.7 ± 0.7*	4.2 ± 1.0	p < 0.05
Doppler E (cm/s)	76 ± 8	85 ± 15	p < 0.05
Doppler A (cm/s)	68 ± 17	48 ± 9	p < 0.01
E:A ratio	1.22 ± 0.4	1.81 ± 0.33	p < 0.01
End-diastolic dimension (cm)	5.0 ± 0.5	5.0 ± 0.5	NS

*Only 23 patients.
A = peak atrial filling velocity; E = peak early filling velocity; NS = not significant.

completion of baseline measures, 23 patients and 15 control subjects with high-quality M-mode echocardiograms received 60 mg of pyridostigmine orally and were restudied 1 hour later by the same protocol as at baseline.

M-mode echocardiographic measures: M-mode recordings of the LV short axis were obtained using 2-dimensional echocardiographic guidance in the parasternal long-axis view. End-diastolic diameter was defined as the peak of the R wave, and end-systolic diameter was defined as the smallest diameter in the corresponding heart cycle. M-mode ejection fraction was calculated according to the method of Teichholtz et al.[20] M-mode peak filling and peak ejection rates were assessed from digitized M-mode recordings using a Graphtec KD 4300 digitizing table (Graphtec Incorp., Tokyo, Japan) interfaced to an IBM personal computer. The time resolution of the digitizing program was 2 milliseconds.

Doppler echocardiographic measures: Using the apical 4-chamber view, pulsed Doppler recordings of the LV mitral inflow velocities were obtained, as previously described.[19] In the subjects who were studied before and after pyridostigmine, care was taken to use the same window and sampling site at both studies.

The diastolic filling period was measured from onset to end of mitral inflow. The isovolumic relaxation period was measured from the end of systolic flow to the onset of diastolic flow. Doppler peak early (E) and atrial (A) inflow velocities in diastole were measured, and the E:A ratio was calculated.

The Doppler measure of LV systolic function was peak aortic outflow velocity obtained from the apical 4-chamber view. All echocardiographic and Doppler measures were calculated as the mean of 8 to 10 beats, avoiding pre- or postextrasystolic beats.

Statistical methods: Results are reported as mean ± standard deviation. Mean values for the study groups were compared by the Wilcoxon rank sum test. The results before and after pyridostigmine were compared by paired Student *t* test. P values <0.05 were considered significant.

RESULTS

High-quality Doppler signals were obtained in all study subjects, but 2 patients with myasthenia did not have M-mode echocardiograms with a quality that allowed digitizing (dropouts of endocardial border). Therefore, peak filling and ejection rates are reported in only 23 patients.

Left ventricular diastolic measures at rest: M-mode peak filling rate was 2.7 ± 0.7 s^{-1} in the group with myasthenia compared with 4.2 ± 1.0 s^{-1} in the control group (p <0.05). E was 76 ± 8 cm/s in the patients compared with 85 ± 18 cm/s in the control group (p <0.05), whereas A was 68 ± 17 and 48 ± 8 cm/s, respectively (p <0.05). As a consequence, the E:A ratio in the patients was 33% less than in the control group (1.22 ± 0.40 vs 1.81 ± 0.33; p <0.001) (Figure 1). Diastolic filling period, isovolumic relaxation period and LV end-diastolic diameter were not significantly different in the 2 study groups (Table I).

Heart rate, blood pressure and left ventricular systolic measures at rest: Heart rate, blood pressure and LV systolic function measures at rest were similar in both groups (Table II).

The effects of pyridostigmine on left ventricular diastolic measures: After pyridostigmine, peak filling rate increased in the group with myasthenia by 20% from 2.7 ± 0.7 to 3.3 ± 0.9 s^{-1} (p <0.01) and E increased by 9% from 76 ± 14 to 83 ± 15 cm/s (p <0.05). A decreased after pyridostigmine by 9% from 68 ± 17 to 62 ± 17 cm/s (p <0.05). Thus, the E:A ratio increased by 17% from 1.22 ± 0.4 to 1.42 ± 0.4 (p <0.01) (Figure 2).

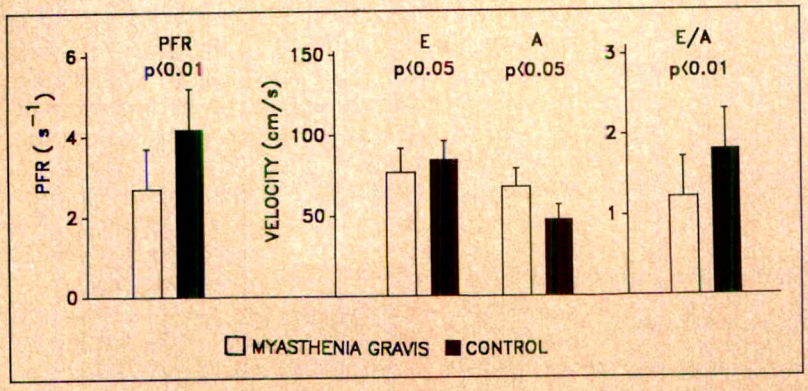


FIGURE 1. M-mode peak filling rate (PFR), Doppler peak early (E) and atrial (A) filling velocities, and E:A ratio in patients with myasthenia gravis and in control group.

Diastolic filling period in the patients was 451 ± 110 ms before and 482 ± 108 ms after pyridostigmine (p = not significant [NS]), and isovolumic relaxation time was 88 ± 14 and 90 ± 12 ms (p = NS), respectively. LV end-diastolic dimension did not change significantly after pyridostigmine (5.0 ± 0.5 vs 4.9 ± 0.5 cm).

Pyridostigmine did not cause any significant changes of the diastolic measures in the control group (Table III).

The effects of pyridostigmine on heart rate, blood pressure and left ventricular systolic function: Heart rates before and after pyridostigmine were 70 ± 12 vs 68 ± 11 beats/min in the group with myasthenia, and 66 ± 6 vs 63 ± 6 beats/min in the control subjects, respectively (p = NS). Systolic and diastolic blood pressures before and after pyridostigmine were 132 ± 11/84 ± 5 vs 130 ± 13/85 ± 6 mm Hg in the patients, and 133 ± 4/87 ± 6 vs 130 ± 12/86 ± 9 in the control subjects, respectively (p = NS), M-mode ejection fractions were 76 ± 8 vs 76 ± 7, and 79 ± 5 vs 81 ± 4%, respectively (p = NS), peak aortic outflow velocity was 109 ± 18 vs 109 ± 14, and 98 ± 13 vs 100 ± 13 cm/s, respectively (p = NS), and peak ejection rate was 1.9 ± 0.4 vs 1.9 ± 0.5, and 2.1 ± 0.4 and 2.0 ± 0.3 s^{-1}, respectively (p = NS).

TABLE II Heart Rate, Blood Pressure and Systolic Variables in 25 Patients with Myasthenia Gravis and in 25 Control Subjects

	Myasthenia Gravis (n = 25)	Control Subjects (n = 25)	p Value
Heart rate	70 ± 12	68 ± 16	NS
Blood pressure (mm Hg)			
Systolic	135 ± 18	138 ± 16	NS
Diastolic	88 ± 6	90 ± 7	NS
Systolic measures			
M-mode ejection fraction (%)	76 ± 8	79 ± 5	NS
Peak aortic outflow velocity (cm/s)	109 ± 18	98 ± 13	NS
M-mode peak ejection rate (s^{-1})	1.9 ± 0.4*	2.1 ± 0.3	NS

*Only 23 patients.
NS = not significant.

DISCUSSION

The current study shows that LV diastolic filling differs significantly in patients with myasthenia gravis compared with that in an age- and heart rate-matched control group. The patients with myasthenia had significantly lower M-mode peak filling rate and E, whereas A was increased. Systolic function was normal in the patients at baseline. The reason for an altered diastolic function in the presence of normal systolic function is unknown, but similar findings in other patient groups have been suggested to reflect an early reduction in cardiac performance.[21,22] However, the significance of this finding in patients with myasthenia gravis needs further study.

Cholinergic activation can elicit a negative atrial inotropy mediated by muscarinic receptors, and positive inotropic effects mediated by nicotinic and nonspecific membrane receptors.[5–8] Myasthenia gravis is an auto-

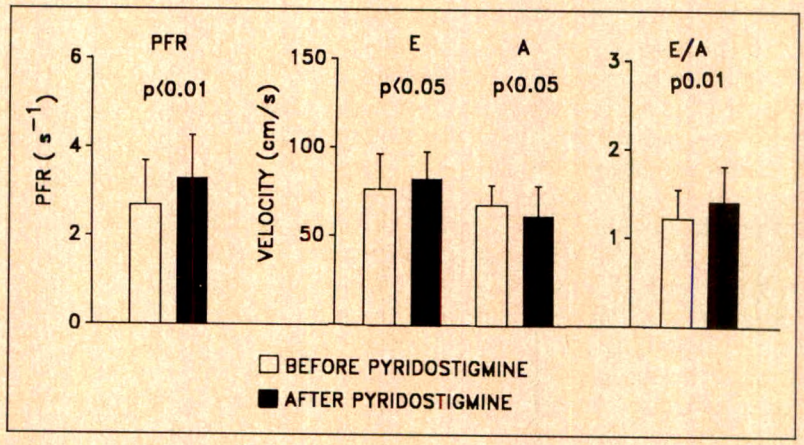


FIGURE 2. M-mode peak filling rate (PFR), Doppler peak early (E) and atrial (A) filling velocities, and E:A ratio in 23 patients with myasthenia gravis before and after 60 mg of pyridostigmine.

TABLE III LV Diastolic Measures in 23 Patients and 15 Control Subjects Before and After Pyridostigmine

	Myasthenia Gravis (n = 23)	Control Subjects (n = 15)	p Value
Diastolic filling periods (ms)	451 ± 110/482 ± 108	456 ± 87/507 ± 70	NS
Isovolumic relaxation time (ms)	88 ± 14/90 ± 12	90 ± 16/85 ± 12	NS
Doppler E (cm/s)	76 ± 14/83 ± 15*	86 ± 14/87 ± 11	NS
Doppler A (cm/s)	68 ± 17/62 ± 17*	54 ± 9/59 ± 5	NS
Doppler E:A ratio	1.2 ± 0.4/1.4 ± 0.4†	1.7 ± 0.2/1.5 ± 0.1	NS
Peak filling rate (s^{-1})	2.7 ± 0.7/3.3 ± 0.9†	4.2 ± 1.0/4.0 ± 1.1	NS

*p < 0.05; †p < 0.01.
Abbreviations as in Table I.

immune disease where the cholinergic activation is influenced by antibodies to nicotinic acetylcholine receptors. However, whether these factors in part may account for the alterations in the diastolic filling measures that were observed in the current study is not clear.

The effect of pyridostigmine on left ventricular diastolic filling: Diastolic filling was significantly altered by intake of the acetylcholine esterase inhibitor pyridostigmine in the patients with myasthenia. After pyridostigmine there was an increase in the early filling measures, and a decrease in the atrial filling velocity. Diastolic measures were not altered in the control group, nor was systolic function altered in any of the groups. The reason for such a differing effect on systolic and diastolic measures is unclear, but diastolic function may be a more sensitive measure of cardiac performance than systolic function.

Pyridostigmine can cause an increment in both circulating acetylcholine and in local acetylcholine in the heart. The fact that we did not observe any changes in diastolic filling measures in the control group after pyridostigmine may indicate that this drug has no direct cardiovascular effects that may influence the measures that we utilized. Whether the apparent cardiovascular effect of pyridostigmine in the patients with myasthenia is associated with the acetylcholine antibodies or is mediated by other mechanisms remains to be shown.

Heart rate and age are important determinants of diastolic measures. With increasing heart rate, E decreases whereas the peak filling rate increases.[19,28] In our patients, both E and the M-mode peak filling rate increased after intake of pyridostigmine. Furthermore, it has previously been reported that alterations in E and A are markedly dependent on the diastolic filling period.[19] This measure was not different in our 2 study groups and was not altered after pyridostigmine. Thus it is unlikely that the observed differences are caused by heart rate changes or alterations in timing measures.

Study limitations: LV diastolic filling may be influenced by age and heart rate,[17–19] filling pressures,[23,24] myocardial ischemia[25,26] and factors that influence LV wall compliance.[27] Several measurements may be used to characterize diastolic function. Although M-mode filling rate and Doppler filling velocities are well documented as measures of diastolic function, noninvasively obtained measures of diastolic function need to be interpreted with care. Furthermore, loading conditions influence diastolic function,[23,24] and they were only measured noninvasively and indirectly in the present study.

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Intravascular Ultrasound Imaging of Saphenous Vein Graft Stenosis

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Coronary angiography has been used as a gold standard for assessing the results of such interventional procedures as balloon angioplasty, atherectomy and laser angioplasty. However, it is still imprecise in defining the extent and composition of atheromatous plaques, and can underestimate the severity of disease process in an eccentric lesion.[1,2] The introduction of intravascular ultrasound as an imaging modality for atherosclerotic coronary artery disease has opened a new field for studying the morphologic changes before and after interventional procedures. Because of the incorporation of high-frequency transducers, it is possible to obtain images of the coronary arterial wall and assess the structural composition of the diseased segments.[3–5] With the increasing number of procedures and devices being developed currently to deal with atherosclerotic obstruction, there is a need for a technique that will permit accurate assessment of alterations in the luminal area, integrity of the intimal surface, and the presence or absence of ulcerated plaques and thrombi. The present study describes our initial experience in using intravascular ultrasound to evaluate stenosed saphenous vein grafts undergoing angioplasty.

Six patients undergoing percutaneous transluminal angioplasty of saphenous vein grafts formed the study group. CVIS ultrasound system (Cardiovascular Imaging Systems, Inc., Sunnydale, California) was used in 3 cases and the Diasonics ultrasound system (Diasonics Inc., Milpitas, California) was used in the other 3 patients. All images were stored on ½-inch video tape for off-line analysis. Hand injections of contrast medium were used to guide the ultrasound catheter to the site of the lesion. Intravascular ultrasound imaging was performed in 2 patients (4 sites) before angioplasty and in the remaining patients (11 sites) after angioplasty or laser therapy.

Ultrasound images were digitized and quantitative measurements of minimal luminal dimensions were obtained at various stenotic sites before and after angioplasty using a commercially available computer system (Nova Microsonics). Angiographic images were also analyzed for measurement of minimal luminal dimension at the same site of the vein that was imaged by ultrasound from a projected cineframe in diastole using electronic digital calipers (Brown and Sharpe Digital Cal Plus model 599-571-3). Ultrasound images were also analyzed for the presence of calcific plaque, plaque fissuring and dissection. Plaque producing an acoustic shadow was defined as calcific.[6]

Ultrasound luminal dimensions were analyzed by 2 independent observers and by the same observer after an interval of 2 weeks for interobserver and intraobserver variability.

Linear regression analysis was used to compare the ultrasound and angiographic measurements. Data were expressed as mean value ± standard error of the estimate (SEE).

A close correlation ($r = 0.96$) was observed between the ultrasound and angiographically measured luminal dimensions in a comparison of 15 sites (Figure 1). Ultrasound luminal dimensions ranged from 1.95 to 4.64 mm (mean 3.00 ± 0.21), whereas angiographic dimensions at the corresponding sites ranged from 1.44 to 5.06 mm (mean 2.93 ± 0.26, Table I). The luminal dimensions of the stenotic lesions increased significantly after angioplasty (Table I and Figure 2). In 1 patient, the luminal size and appearance of an eccentric atherosclerotic plaque varied with minimal changes in the ultrasound transducer position, most likely due to the altered orientation of the ultrasonic plane in relation to the plaque (Figure 3). Both intra- and interobserver variability was low. The intra- and interobserver correlation coefficients (r) for ultrasound luminal dimensions were 0.99, SEE = 0.03 mm and 0.99, SEE = 0.04 mm, respectively.

The saphenous vein graft lumen and the vessel walls were visualized in all the patients studied. Three patients

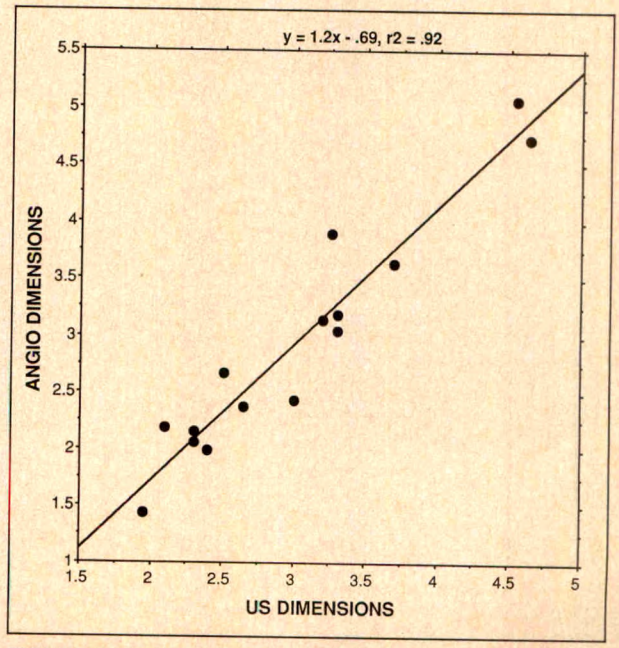


FIGURE 1. Intravascular ultrasound (US) measurements (in millimeters) of saphenous vein graft luminal dimensions correlated with those obtained by angiography (ANGIO). The r value is 0.96.

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(cases 1, 5, 6; Table I) showed the presence of a calcific plaque with acoustic shadowing at the lesion site, which was not obvious from the angiographic film (Figure 4). After angioplasty, a dissection flap could be clearly visualized in 4 patients (Figure 5). In 2 of these patients, a dissection flap could be demonstrated on angiography. In the other 2 patients, no evidence of dissection could be found even on close examination of the angiographic film (Table I). Contrast injections using radioopaque dye during ultrasound imaging helped delineate the true lumen in patients with calcific plaque as well as in those with dissection. In 2 patients, plaque disruption or fissuring was noted by intravascular ultrasound after angioplasty.

The present study demonstrates that intravascular ultrasound imaging of saphenous vein grafts is feasible and provides information regarding the characteristics of the vessel wall. The minimal ultrasound luminal dimensions

TABLE I Intravascular Ultrasound Imaging of Saphenous Vein Graft Stenosis

Pt. No.	Age/I (yr)	Dimension (mm) Before Angioplasty		Dimension (mm) After Angioplasty		Dis		Ca	
		U	A	U	A	U	A	U	A
1	64/9	2.10, 2.30, 2.65	2.19, 2.06, 2.38	3.0, 3.30, 3.69	2.43, 3.05, 3.63	0	0	+	0
2	66/7	—	—	2.30, 3.30, 4.64	2.15, 3.18, 4.72	+	0	0	0
3	55/7	—	—	4.54	5.06	+	+	0	0
4	55/6	—	—	2.40, 3.25	1.99, 3.89	+	+	0	0
5	61/5	1.95	1.44	3.20	3.16	+	0	+	0
6	66/10	—	—	2.51	2.67	0	0	+	0

A = angiography; Ca = calcified plaque; Dis = saphenous vein graft dissection; I = interval in years between coronary artery bypass surgery and saphenous vein angioplasty; U = intravascular ultrasound; + = present; 0 = absent; – = not done.

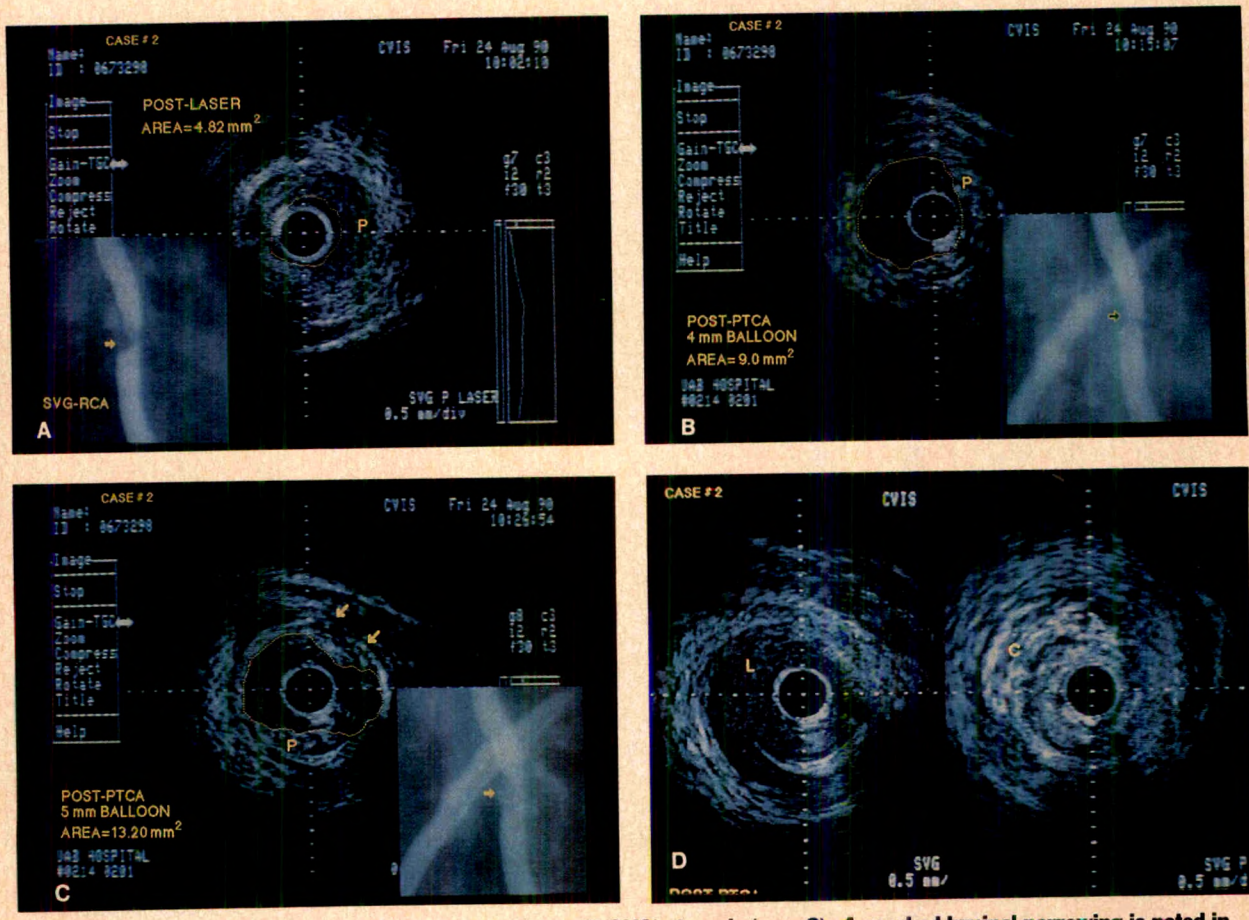


FIGURE 2. Intravascular ultrasound in saphenous vein graft (SVG) stenosis (case 2). *A*, marked luminal narrowing is noted in the graft that was imaged after excimer laser ablation using a 2.0 mm diameter laser catheter (A.I.S., Inc.). The luminal area measured 4.82 mm². *B*, the luminal area increased to 9 mm² after a 4 mm balloon dilatation. *C*, subsequent dilatation using a 5 mm balloon increased luminal area to 13.20 mm² and resulted in detectable plaque (P) disruption *(arrows)*. *D*, a small injection of radioopaque contrast through guiding catheter during intravascular imaging results in appearance of multiple tiny bright contrast (C) echoes that help delineate the vessel lumen (L). PTCA = percutaneous transluminal coronary graft; RCA = right coronary artery.

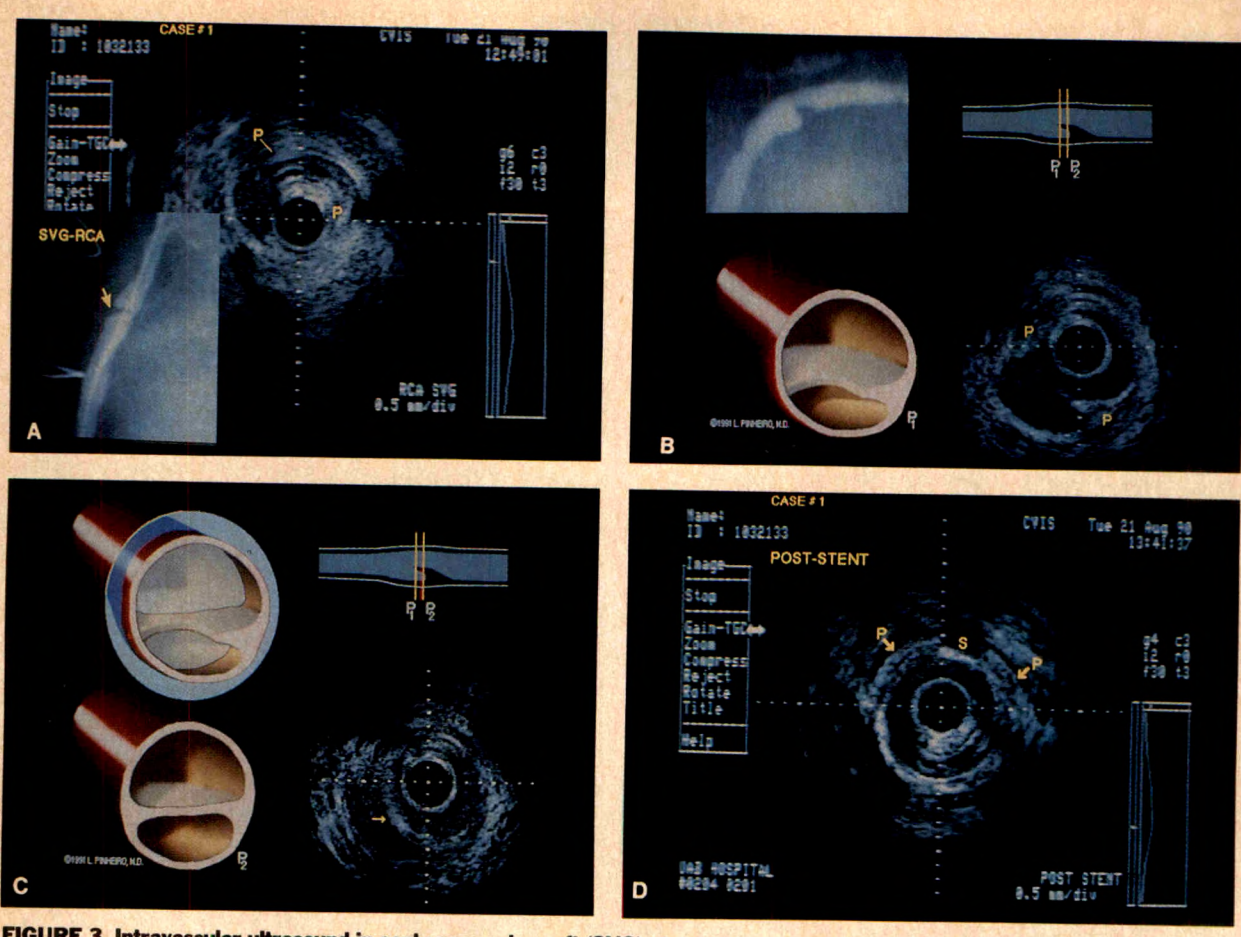


FIGURE 3. Intravascular ultrasound in saphenous vein graft (SVG) stenosis (case 1). *A*, significant narrowing produced by an atherosclerotic plaque (P) in proximal segment of the graft to the right coronary artery (RCA). *B* and *C*, significant narrowing in distal portion of the same graft. Luminal size and appearance of plaque (P in B, *arrow* in C) varied with minimal change in ultrasound transducer position. Schematics illustrate how this could occur with an eccentric plaque of the type seen in this patient. P_1 and P_2 represent 2 sections taken at different levels of the plaque. Minimal luminal area was 5.10 mm^2. *D*, increase in size of the lumen to 7.24 mm^2 after angioplasty and stent placement. Plaque disruption is clearly noted *(arrows)*. A portion of the stent is seen as a bright linear echo (S).

of the stenotic sites measured both before and after angioplasty correlated highly with those estimated by angiography. In the current study, ultrasound imaging could demonstrate the presence of heavy calcium in some of the atherosclerotic plaques, which was not detected angiographically. The importance of calcific deposits in atherosclerotic saphenous vein grafts has not been well studied but may be a factor in determining the success of angioplasty or newer atherectomy or laser techniques. Ultrasound definition of the presence of calcium in the plaque may help in determining the interventional technique to be used. In addition, intravascular ultrasound may be superior to conventional angiography in detecting intimal dissection, since in 2 of our 4 patients with ultrasonic delineation of the dissection flap after angioplasty, no evidence of dissection could be found even on close scrutiny of the angiogram. Development of intimal dissection increases the risk of acute closure[7] and may influence the decision to place an intravascular stent. Intravascular ultrasound imaging has the potential of becoming an important adjunct to angiography in identifying patients

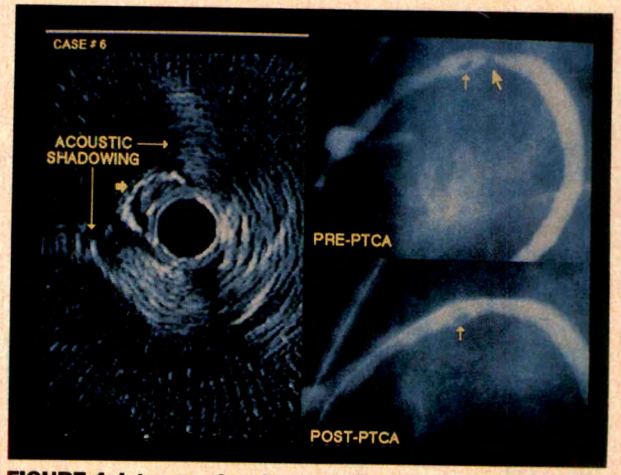


FIGURE 4. Intravascular ultrasound in saphenous vein graft stenosis (case 6) demonstrating severe graft lumen stenosis, as well as a calcified plaque *(bold arrow)* producing acoustic shadowing. The *large arrow* on the angiogram denotes stenosis; the *small arrows* represent a plaque. PTCA = percutaneous transluminal coronary graft.

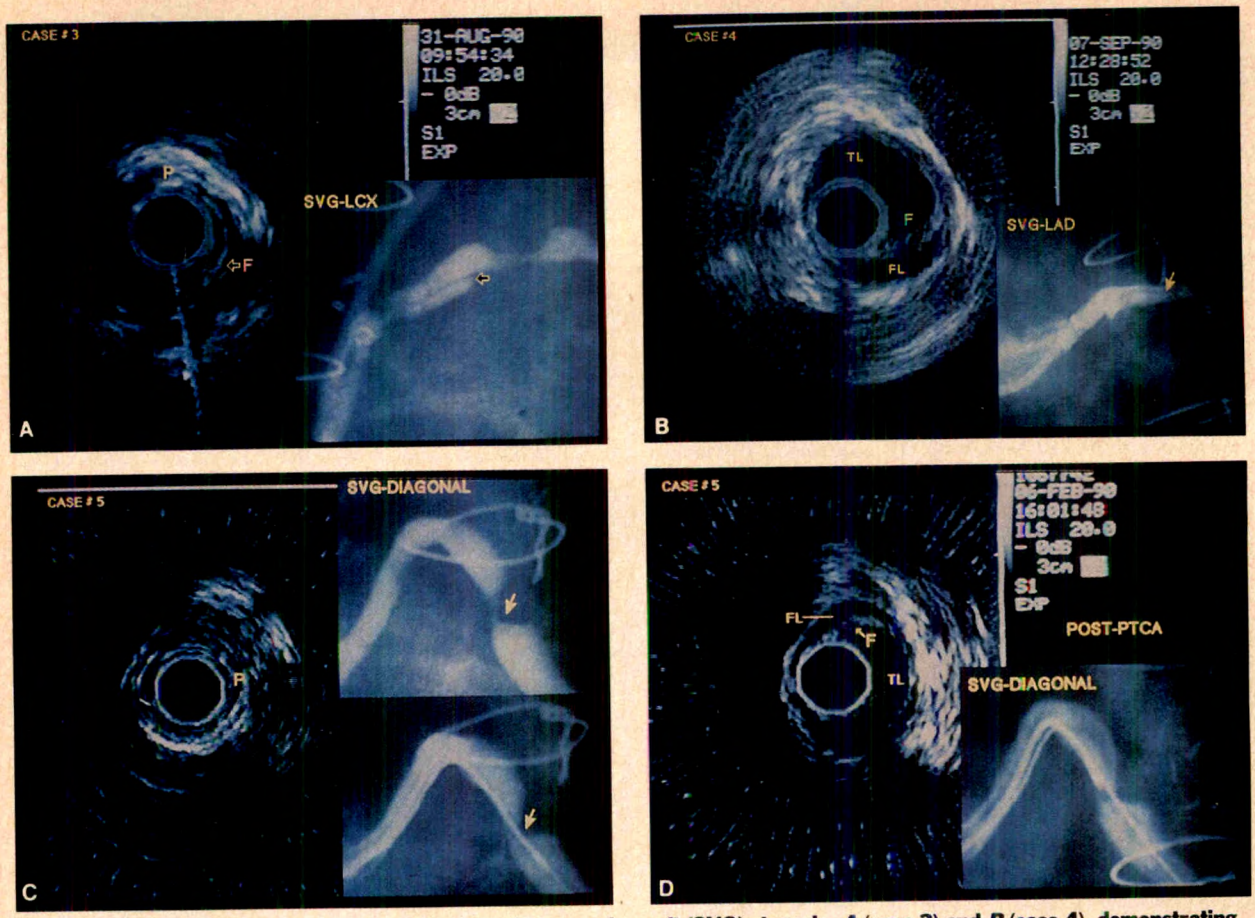


FIGURE 5. Intravascular ultrasound imaging in saphenous vein graft (SVG) stenosis. *A* (case 3) and *B* (case 4), demonstrating the presence of an intimal dissection flap (F) imaged after balloon dilatation. Dissection in these 2 patients was also noted angiographically. *C* and *D* (case 5), showing the development of intimal dissection after balloon dilatation of a severely narrowed graft lumen (C). The angiographic film did not reveal any evidence of dissection. FL = false lumen; LAD = left anterior descending artery; LCX = left circumflex artery; TL = true lumen.

with an increased risk of early and late complications, thus assisting the cardiologist in selecting the most appropriate interventional procedure based on the lesion characteristics.

These results demonstrate the feasibility of using intravascular ultrasound to delineate atherosclerotic narrowing of saphenous vein grafts as well as in defining changes occurring in lumen size after the interventional procedure. The accuracy of intravascular ultrasound in the assessment of saphenous vein graft luminal dimension appears to be high and is comparable to that obtained for native coronary arteries.[5] In addition, the technique may be superior to angiography in detecting plaque calcium as well as intimal dissection, both of which may have prognostic and therapeutic implications. Although our initial results are promising, more subjects with varied lesion morphology are needed to define the exact role of this technique in the assessment of patients with saphenous vein graft stenosis undergoing angioplasty.

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Prognostic Significance of Silent Ischemia in Elderly Patients with Peripheral Arterial Disease With and Without Previous Myocardial Infarction

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Early postoperative silent myocardial ischemia detected by ambulatory electrocardiography (ECG) in patients undergoing peripheral vascular surgery for occlusive peripheral arterial disease (PAD) is associated with clinical ischemic events after surgery.[1] Patients undergoing peripheral vascular surgery who had silent myocardial ischemia before surgery detected by ambulatory ECG had an increased incidence of major postoperative cardiac events after surgery.[2] At a mean follow-up of 615 days after peripheral vascular surgery, cardiac events occurred in 12 of 32 (38%) patients with ischemia before surgery detected by ambulatory ECG and in 10 of 144 (7%) without myocardial ischemia (relative risk 5.4).[3] We are reporting data from a prospective study correlating silent myocardial ischemia detected by 24-hour ambulatory ECG with the incidence of new coronary events at a 43-month mean follow-up in elderly patients with PAD and coronary artery disease (CAD) and in those with PAD and hypertension, valvular heart disease or cardiomyopathy without CAD.

Symptomatic PAD was diagnosed if the patient had a documented history of surgery for PAD or if the patient had ischemic pain at rest, ulceration or gangrene in an extremity, intermittent claudication, numbness, coldness, cyanosis or pallor in an extremity, or trophic changes with dry, scaly and shiny atrophic skin, diminished hair growth, thickened, brittle toenails, or subcutaneous atrophy in an extremity associated with absent or weak arterial pulses palpated by ≥2 physicians.[4]

Patients were considered at entry into the study to have CAD if they had a documented clinical history of myocardial infarction, or electrocardiographic evidence of Q-wave myocardial infarction (156 patients), or typical angina pectoris without previous myocardial infarction (4).

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In a prospective study, ambulatory ECG was performed for 24 hours using portable Avionics tape recorders (model 445) to obtain 2 leads corresponding to a modified V_1 and V_5 in 357 elderly patients with symptomatic PAD. The tapes were analyzed using a Cardio-Data Mk 3 computer system. ST-segment changes were written out on electrocardiographic paper at a speed of 25 mm/s and interpreted by 2 cardiologists. Patients with marked ST-segment depression (≥1.5 mm) at rest were excluded from the study. Silent ischemia was diagnosed if horizontal or downsloping ST-segment depression ≥1.0 mm below the level at rest occurred at 80 ms after the J point, lasted for ≥1.0 minute and was unassociated with anginal symptoms. If ST-segment depression at rest occurred, an additional 2.0 mm of ischemic ST-segment depression below the level at rest at 80 ms after the J point was needed. Complex ventricular arrhythmias included ventricular tachycardia or paired, multiform or frequent (≥30/hour) ventricular premature complexes.

Technically satisfactory 24-hour ambulatory ECG was performed in 291 of 357 (82%) patients. The 291 patients included 95 men and 196 women (mean age 82 ± 8 years, range 62 to 98). Of 291 patients with PAD, 160 (55%) had CAD, and 131 (45%) had systemic hypertension, valvular heart disease or cardiomyopathy without clinical evidence of CAD.

Mean follow-up from the day 24-hour ambulatory ECG was performed was 43 ± 20 months (range 3 to 67). New coronary events were diagnosed if the patient developed myocardial infarction, primary ventricular fibrillation or sudden cardiac death. Myocardial infarction was documented as previously described.[5] *Sudden cardiac death was defined as an unexpected cardiac death in a patient with CAD, systemic hypertension, valvular heart disease or cardiomyopathy within 1 hour of being clinically stable.*[6] *All coronary events and causes of death were reviewed by the senior investigator, with the physician taking care of the patient.*

Chi-square analyses were used to analyze data (Tables I and II). Survival curves for coronary events in

TABLE I Correlation of Silent Ischemia with Incidence of New Myocardial Infarction, Sudden Cardiac Death and New Coronary Events at 43-Month Follow-Up in Elderly Patients with Peripheral Arterial and Heart Disease

	Myocardial Infarction (%)		Sudden Cardiac Death (%)		Coronary Events (%)	
	SI	No SI	SI	No SI	SI	No SI
PAD and CAD	28/60 (47)†	31/100 (31)	26/60 (43)†	28/100 (28)	54/60 (90)*	59/100 (59)
PAD without CAD	8/26 (31)†	15/105 (14)	10/26 (38)†	19/105 (18)	18/26 (69)*	34/105 (32)

*$p < 0.001$; †$p < 0.05$.
CAD = coronary artery disease; PAD = peripheral arterial disease; SI = silent ischemia.

TABLE II Correlation of Number of Episodes of Silent Ischemia, Maximal ST-Segment Depression and Duration of Silent Ischemia with Incidence of New Coronary Events in Elderly Patients with Peripheral Arterial and Heart Disease

	Coronary Events (%)	p Value
≥ 5 episodes/day of SI	15/16 (94)	NS
1 to 4 episodes/day of SI	57/70 (81)	
≥ 2.0 mm of maximal ST-segment depression	41/44 (93)	< 0.02
1.0 to 1.9 mm of maximal ST-segment depression	31/42 (74)	
≥ 60 minutes/day of SI	42/47 (89)	NS
1 to 59 minutes/day of SI	30/39 (77)	

NS = not significant; SI = silent ischemia.

TABLE III Prognostic Variables for Coronary Events and Their Regression Coefficients in the Multivariate Cox Regression Model

Variable	Regression Coefficient	Standard Error	p Value	Relative Risk
Silent ischemia	1.160	0.175	0.000	3.191
Prior CAD	1.008	0.180	0.000	2.740
Systemic hypertension	0.489	0.174	0.005	1.631
Serum triglycerides	−0.004	0.002	0.012	0.997
Cigarette smoking	0.483	0.223	0.037	1.620
Serum high-density lipoprotein cholesterol	−0.014	0.007	0.048	0.986
Obesity	0.454	0.263	0.098	1.575
Age	0.016	0.011	0.148	1.016
Sex*	0.199	0.180	0.265	1.221
Diabetes mellitus	0.210	0.197	0.293	1.233
Serum total cholesterol	0.002	0.002	0.395	1.002
Complex ventricular arrhythmias	−0.033	0.180	0.855	0.968

*Sex = 0 if men and 1 if women.
CAD = coronary artery disease.

patients with CAD, with and without silent ischemia (Figure 1), and for coronary events in those without CAD, with and without silent ischemia (Figure 2), were estimated using the Kaplan-Meier product limit estimator and tested for homogeneity with the log-rank and Wilcoxon tests. The relation between 12 prognostic variables and time to development of coronary events was analyzed using the multivariate Cox regression model (Table III).

Silent ischemia was present in 60 of 160 (38%) patients with PAD and CAD, and in 26 of 131 (20%) with PAD and systemic hypertension, valvular heart disease or cardiomyopathy without CAD. At a mean 43-month follow-up, new coronary events occurred in 165 of 291 (57%) patients. Table I shows the correlation of silent ischemia with new myocardial infarction, sudden cardiac death (including death due to primary ventricular fibrillation) and new coronary events in elderly patients with PAD and CAD and in those with PAD and systemic hypertension, valvular heart disease or cardiomyopathy without CAD. Table I also lists levels of statistical significance and risk ratios.

Table II indicates the correlation of number of episodes of silent ischemia, degree of maximal ST-segment depression, and duration of silent ischemia in elderly patients with PAD and heart disease with new coronary events. Table II also lists levels of statistical significance. Both the log-rank and Wilcoxon tests show that the 2 survival curves for the development of coronary events are significantly different ($p = 0.0000$) between the patient groups with and without silent ischemia for patients with (Figure 1) and without (Figure 2) CAD, respectively. Table III lists 12 prognostic variables for new coronary events and their regression coefficients in the multivariate Cox regression model.

Patients with unstable angina pectoris,[7,8] at high-risk after infarction,[9] with prior myocardial infarction,[10,11] with stable angina pectoris,[12,13] undergoing peripheral

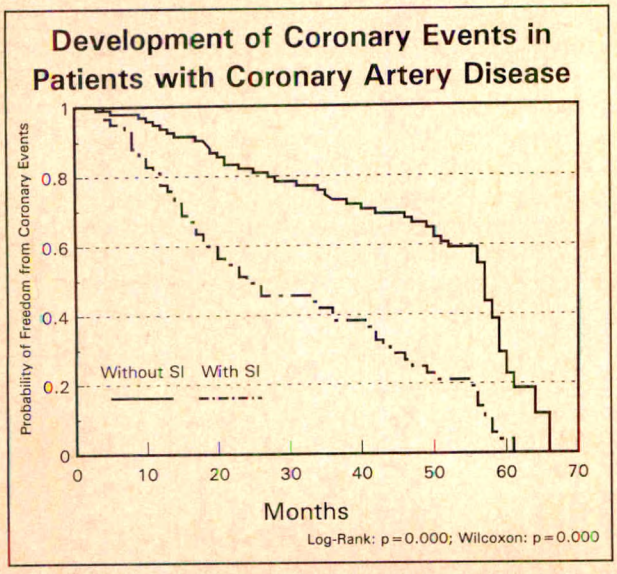


FIGURE 1. Kaplan-Meier survival curves for development of coronary events in patients with peripheral arterial and coronary artery disease, with and without silent ischemia (SI).

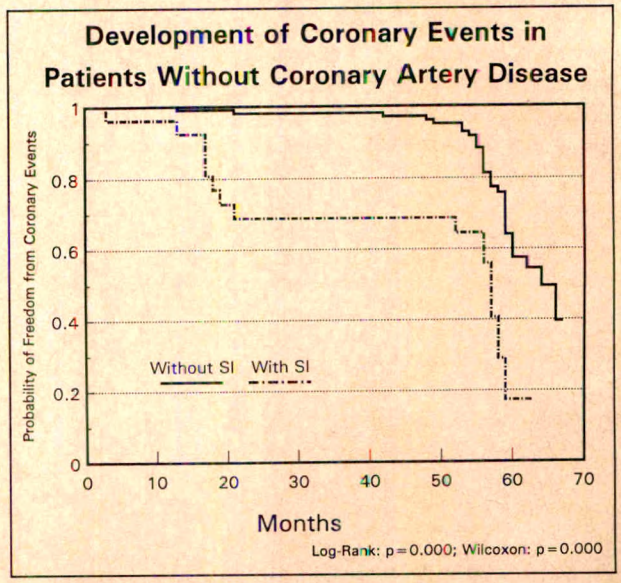


FIGURE 2. Kaplan-Meier survival curves for development of coronary events in patients with peripheral arterial and heart disease without coronary artery disease, with and without silent ischemia (SI).

vascular surgery[1-3] with silent myocardial ischemia detected by ambulatory ECG, and elderly patients with systemic hypertension, valvular heart disease or cardiomyopathy without CAD[11] have an increased incidence of cardiovascular morbidity and mortality. The results from our prospective study of 291 elderly patients with symptomatic PAD showed that silent myocardial ischemia detected by 24-hour ambulatory ECG was associated with an increased incidence of new myocardial infarction, sudden cardiac death and new coronary events in patients with CAD (98% after infarction) and in those with systemic hypertension, valvular heart disease or cardiomyopathy without clinical evidence of CAD. In patients with silent ischemia, the incidence of new coronary events was increased in those with ≥2.0 mm of maximal ST-segment depression compared with that in those with 1.0 to 1.9 mm of maximal ST-segment depression. However, the incidence of new coronary events was not significantly different in patients with ≥5 episodes of silent ischemia/day compared with those with <5 episodes/day or in those with ≥60 minutes/day of silent ischemia compared with those with 1 to 59 minutes/day.

In our previous investigation,[11] multivariate analysis was not performed. In the present study, multivariate analysis showed that silent ischemia was the most important independent risk factor for new coronary events in our elderly population with PAD. After controlling for other prognostic variables, patients with silent ischemia had a 3.2 times greater chance of developing new coronary events than did those without silent ischemia.

Patients with PAD should undergo adequate exercise testing to determine if they have myocardial ischemia and are at increased risk for new coronary events. Patients with PAD who often are unable to perform adequate exercise tests should undergo 24-hour ambulatory ECG, dipyridamole or adenosine-thallium imaging, or stress echocardiography using dipyridamole to determine if they have myocardial ischemia and are at increased risk for new coronary events. Patients with symptomatic PAD and silent ischemia should be treated with antiischemic therapy. Aggressive antiischemic therapy should be considered for patients undergoing peripheral vascular surgery. Whether medical or surgical treatment of silent myocardial ischemia can improve the long-term prognosis of these patients and how much reduction in silent ischemia may be clinically relevant remains to be determined by future studies.

1. Ouyang P, Gerstenblith G, Furman WR, Golueke PJ, Gottlieb SO. Frequency and significance of early postoperative silent myocardial ischemia in patients having peripheral vascular surgery. *Am J Cardiol* 1989;64:1113–1116.

2. Raby KE, Goldman L, Creager MA, Cook EF, Weisberg MC, Whittemore AD, Selwyn AP. Correlation between preoperative ischemia and major cardiac events after peripheral vascular surgery. *N Engl J Med* 1989;321:1296–1300.

3. Raby KE, Goldman L, Cook EF, Rumerman J, Barry J, Creager MA, Selwyn AP. Long-term prognosis of myocardial ischemia detected by Holter monitoring in peripheral vascular disease. *Am J Cardiol* 1990;66:1309–1313.

4. Aronow WS, Sales FF, Etienne F, Lee NH. Prevalence of peripheral arterial disease and its correlation with risk factors for peripheral arterial disease in elderly patients in a long-term health care facility. *Am J Cardiol* 1988;62:644–646.

5. Aronow WS. Prevalence of presenting symptoms of recognized acute myocardial infarction and of unrecognized healed myocardial infarction in elderly patients. *Am J Cardiol* 1987;60:1182.

6. Roberts WC. Sudden cardiac death: definitions and causes. *Am J Cardiol* 1986;57:1410–1413.

7. Nademanee K, Intarachot V, Josephson MA, Rieders D, Mody FV, Singh BN. Prognostic significance of silent myocardial ischemia in patients with unstable angina. *J Am Coll Cardiol* 1987;10:1–9.

8. Gottlieb SO, Weisfeldt ML, Ouyang P, Mellits ED, Gerstenblith G. Silent ischemia predicts infarction and death during 2 year follow-up of unstable angina. *J Am Coll Cardiol* 1987;10:756–760.

9. Gottlieb SO, Gottlieb SH, Achuff SC, Baumgardner R, Mellits ED, Weisfeldt ML, Gerstenblith G. Silent ischemia on Holter monitoring predicts mortality in high-risk postinfarction patients. *JAMA* 1988;259:1030–1035.

10. Tzivoni D, Gavish A, Zin D, Gottlieb S, Moriel M, Keren A, Banai S, Stern S. Prognostic significance of ischemic episodes in patients with previous myocardial infarction. *Am J Cardiol* 1988;62:661–664.

11. Aronow WS, Epstein S. Usefulness of silent myocardial ischemia detected by ambulatory electrocardiographic monitoring in predicting new coronary events in elderly patients. *Am J Cardiol* 1988;62:1295–1296.

12. Rocco MB, Nabel EG, Campbell S, Goldman L, Barry J, Mead K, Selwyn AP. Prognostic importance of myocardial ischemia detected by ambulatory monitoring in patients with stable coronary artery disease. Circulation 1988;78: 877–884.

13. Tzivoni D, Weisz G, Gavish A, Zin D, Keren A, Stern S. Comparison of mortality and myocardial infarction rates in stable angina pectoris with and without ischemic episodes during daily activities. *Am J Cardiol* 1989;63:273–276.

The Most Prolific Author

During morning rounds, a junior medical student asked a pertinent question regarding ventilatory management in a postoperative patient. To stimulate further thought in the matter, we asked him to perform a literature search on the subject in question. On the following day he stated that the author who appeared to be most knowledgeable was named "et al." On further review it became quite evident that "et al" was indeed a well respected authority on the subject. In fact, his credits included over 16,000 medical publications, 531 publications on topics in physics, astronomy and engineering, and 160 publications in the humanities. After some time we were able to locate "et al" on the west coast. He was quite gracious in sending us his 1,390-page curriculum vitae. He stated that his life has been full of excitement dating back to the Paston letters.* During our brief conversation, "et al" repeatedly emphasized his willingness to assist others in their scholarly pursuit as is evident by always appearing last on their publications. To further complicate matters, "et al" informed us of his daughter ("et aliae") who is also quite prolific and happens to practice law. Currently her resume (600 pounds) includes 48,333 pages of text citing over 580,000 references to civil and federal cases. It appears quite evident that she also demonstrates the scholarly family work ethics. We can only hope that their future offspring continue to be as productive.

John M. Palmisano, RRT
Ann Arbor, Michigan
25 July 1991

Letters (from the United States) concerning a particular article in the *Journal* must be received within 2 months of the article's publication, and should be limited (with rare exceptions) to 2 double-spaced typewritten pages. Two copies must be submitted.

*It is believed that the term "et al" first came into use in the Paston letters. The Paston letters were carefully preserved letters of their family correspondence. These letters have provided us with a detailed description of the social life and political history of the 15th century.

Correction

In the brief report, "Lack of Pain During Myocardial Infarction in Diabetics — Is Automonic Function Responsible?" by Acharya et al in the September 15, 1991 issue, pages 793 and 795, the Table I, column 3 heading should read "Duration of Diabetes (yrs)," not "(mos)" as written. In Table II, the headings for the first 2 rows of listed p values have been mistakenly reversed. The first heading should read, "Control Versus Painless," and the second heading should read, "Control Versus Painful."

Some Good Cardiologic Books Published in 1991

MAJOR TEXTBOOKS

1. Braunwald E, editor. *Heart Disease. A Textbook of Cardiovascular Medicine.* Philadelphia: WB Saunders Company, 1992:1918, $110.00 (single volume), $125.00 (double volume).

2. Chatterjee K, Cheitlin MD, Karliner J, Parmley WW, Rapaport E, Scheinman M, editors. *CARDIOLOGY. An Illustrated Text/Reference, Volume 1, Physiology, Pharmacology, Diagnosis* (approximately 1400 pages) and *Volume 2, Cardiovascular Disease* (approximately 1320 pages). Philadelphia: JB Lippincott, and New York: Gower Medical Publishing, 1991: approximately 2720 pages, $225.00 (both volumes).

3. Giuliani ER, Fuster V, Gersh BJ, McGoon MD, McGoon DC, editors. *Cardiology: Fundamentals and Practice*, Second Edition. St. Louis: Mosby Year Book, 1991:2261 (Volumes 1 and 2), $125.00.

All 3 are good. One originates from Boston (Harvard), 1 from San Francisco (University of California), and 1 from Rochester, Minnesota (Mayo Clinic). I prefer the Braunwald book because it contains the most information proportional to size and price. Each page is fully packed. Although it has 69 contributors, Braunwald is the author or coauthor of 23 (37%) of the 62 chapters, and he vigorously edited the other 39 (63%). Although the Braunwald book now has single-colored lines in illustrations, reddish background for tables, and red subheadings, the Chatterjee et al book has taken color much further to produce a beautiful 2-volume text on thick paper. The tradeoff, however, is that the Chatterjee text is twice the cost of the Braunwald book. The Chatterjee text actually represents a hardbound edition of the looseleaf *Cardiology* text edited by Drs. William Parmley and Kanu Chatterjee, published originally in 1987 and updated yearly since. The Giuliani book is a single institution one that is in the price range of the Braunwald book. All 3 texts are heavy, especially the Chatterjee one. If any of these volumes slip off a desk they can break a toe.

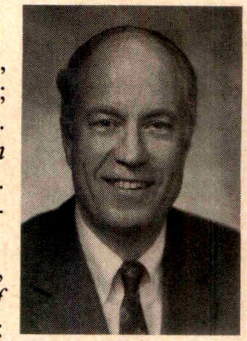
4. Fozzard HA, Haber E, Jennings RB, Katz AM, Morgan HE, editors. *The Heart and Cardiovascular System. Scientific Foundations.* Second Edition. Volumes I and II. New York: Raven Press, 1991:2335, $340.00.

These 2 volumes provide comprehensive reviews of principles and methods of cardiovascular research. The first edition was well received and this second edition looks even more comprehensive.

5. Flyer DC, editor. *Nadas' Pediatric Cardiology.* Philadelphia: Hanley & Belfus (also St. Louis: Mosby Year Book), 1992:784, $75.00.

Although it has Dr. Alexander S. Nadas' name in the title, this book represents a near complete new text and is written to honor Dr. Nadas who was chief to most of the contributors to this volume. The book remains easily readable. If one has a single textbook on pediatric cardiology, I would vote for this one, which is reasonably priced.

CARDIAC IMAGING



6. Marcus ML, Skorton DJ, Schelbert HR, Wolf GL, editors; Braunwald E, consulting editor. *Cardiac Imaging. A Companion to Braunwald's Heart Disease.* Philadelphia: WB Saunders Company, 1991:1318, $110.00.

7. Pohost GM, O'Rourke RA, editors. *Principles and Practice of Cardiovascular Imaging.* Boston: Little, Brown and Company, 1991:880, $175.00.

The Marcus book has 118 contributors and is published in the same format as the Braunwald book. Thus, each page is fully packed. The Pohost book, which costs 38% more and has 33% fewer pages, is also well-done. The best value here clearly is the Marcus book.

8. Elliott LP, editor. *Cardiac Imaging in Infants, Children, and Adults.* Philadelphia: JB Lippincott, 1991:927, $150.00.

This book focuses primarily on angiography and would appeal most to radiologists.

9. Gerson MC, editor. *Cardiac Nuclear Medicine.* Second Edition. New York: McGraw-Hill, Inc., 1991: 653, $100.00.

A good book by 37 contributors.

10. Gutierrez FR, Brown JJ, editors. *Cardiovascular Magnetic Resonance Imaging.* St. Louis: Mosby Year Book, 1992:233, $99.00.

Magnetic resonance imaging represents 1 of the most significant advances in diagnostic imaging in the last decade. This book from the Mallinckrodt Institute of Radiology summarizes current use and future applications of this technique to the cardiovascular system.

THROMBOSIS AND THROMBOLYSIS

11. Fuster V, Verstraete M, editors. *Thrombosis in Cardiovascular Disorders.* Philadelphia: WB Saunders Company, 1992:565, $95.00.

A superb and much needed book by 47 contributors. The best book so far on this subject.

12. Haber E, Braunwald E, editors. *Thrombolysis. Basic Contributions and Clinical Progress.* St. Louis: Mosby Year Book, 1991:357, $57.00.

Drs. Haber and Braunwald served as chairmen of a symposium on thrombolysis sponsored by the National Heart, Lung, and Blood Institute. The 25 chapters in this book are updates of presentations at that symposium. This book is loaded with information on thrombolysis, as one might expect from the editors and the sponsor.

CORONARY ARTERY DISEASE

13. Roberts R, editor. *Coronary Heart Disease and Risk Factors.* Mount Kisco: New York, 1991:346, $59.00.

A quick update book by 21 authors, 14 from Roberts' Baylor College of Medicine.

14. Redmond GP, editor. *Lipids and Women's Health*. New York: Springer-Verlag, 1991:260, $49.00.

A timely book with 14 contributors.

15. Rifkind BM, editor. *Drug Treatment of Hyperlipidemia*. New York: Marcel Dekkar, Inc., 1991:270, $79.75.

A timely book on lipid-lowering therapy by 11 experts in this field.

16. Goldberger AL. *Myocardial Infarction. Electrocardiographic Differential Diagnosis*. Fourth Edition with 210 illustrations. St. Louis: Mosby Year Book, 1991:386, $49.95.

This book focuses on the electrocardiogram in myocardial infarction and its electrocardiographic simulators. As such, it is comprehensive, authoritative and well-done.

17. Rutherford JD, editor. *Unstable Angina*. New York: Marcel Dekker, Inc., 1992:301, $89.75.

Dr. Eugene Braunwald in the foreword states that 750,000 patients are admitted to hospitals in the U.S. each year with unstable angina pectoris and that almost 100,000 each year develop acute myocardial infarction within 1 month after onset of unstable angina. Thus, a single book on a common problem is useful.

18. Abrams J, Pepine CJ, Thadani U, editors. *Medical Therapy of Ischemic Heart Disease. Nitrates, Beta Blockers, and Calcium Antagonists*. Boston: Little, Brown and Company, 1992:527, $75.00.

These 16 contributors and leaders in cardiovascular therapeutics provide a useful book.

19. Leier CV, editor. *Cardiotonic Drugs. A Clinical Review*. Second Edition. New York: Marcel Dekker, 1991:362, $115.00.

A good book on the positive inotropic agents, those that increase cardiac contractility.

20. Vlay SC, editor. *Medical Care of the Cardiac Surgical Patient*. Boston: Blackwell Scientific Publications, 1992:331, $29.95.

The least expensive book of quality in the present list. Very useful. Can be placed in the doctor's white coat.

21. Wenger NK, Hellerstein HK, editors. *Rehabilitation of the Coronary Patient*. Third Edition. New York: Churchill Livingstone, 1992:625, $74.95.

An excellent book with 44 contributors. Much expanded compared with the second edition.

ECHOCARDIOGRAPHY

22. Clements FM, de Bruijn NP. *Transesophageal Echocardiography*. Boston: Little, Brown and Company, 1991:163, $105.00.

23. Sutherland GR, Roelandt Jos RTC, Fraser AG, Anderson RH. *Transesophageal Echocardiography in Clinical Practice*. London: Gower Medical Publishing, 1991: approximately 120 pages, $167.00.

Clements and de Bruijn perform approximately 150 transesophageal echocardiographic studies yearly in awake patients and approximately 500 yearly in the operating room at Duke University. Their first book on this subject appeared in 1987, and at the time, I believe, their book was the first on the subject. This second one now has much competition, but it is still good. The Sutherland et al book is nicely prepared with lots of color illustrations, but its price is 38% more and it has 26% fewer pages than the Clements-de Bruijn book.

ELECTROCARDIOGRAPHY AND ELECTROPHYSIOLOGY

24. Rowlands DJ. *Clinical Electrocardiography*. London: Gower Medical Publishing, 1991:615, $109.00.

A beautifully prepared book in which nearly all of the many illustrations are in color.

25. Fisch C, Surawicz B, editors. *Cardiac Electrophysiology and Arrhythmias*. New York: Elsevier, 1991: 488, $84.00.

26. Naccarelli GV, editor. *Cardiac Arrhythmias: A Practical Approach*. Mount Kisco, New York: Futura Publishing Company, 1991:583, $70.00.

27. Dangman KH, Miura DS, editors. *Electrophysiology and Pharmacology of the Heart. A Clinical Guide*. New York: Marcel Dekker, Inc., 1991:756, $175.00.

The Fisch book is a comprehensive update of present knowledge in the broad field of investigative and practical electrocardiology by 69 contributors.

Dr. Douglas P. Zipes in the foreword of the Naccarelli book states, "While several texts have been published recently that encompass a wide area of cardiac electrophysiology, none have been devoted solely to a practical approach to arrhythmia management." Such is the edited book by Naccarelli and 43 experts in the field.

The Dangman-Miura book by 55 contributors is divided into 4 parts: Part I discusses the 4 major techniques used to investigate the electrical behavior of the heart; Part II discusses electrophysiology of the 5 major types of excitable tissue in the heart; Part III, the common laboratory models of cardiac arrhythmias; and Part IV, the positive inotropic agents and antiarrhythmic drugs. The price is outrageous.

28. Falk RH, Podrid PJ, editors. *Atrial Fibrillation. Mechanisms and Management*. New York: Raven Press, 1992:428, $95.00.

The authors estimate that 1 or 2 million persons living in the U.S. have atrial fibrillation of nonvalvular etiology. Thus, the subject is a very important one, and this entire book is devoted to various aspects of this arrhythmia. It is well done and will be useful.

29. El-Sherif N, Turitto G. *High-Resolution Electrocardiography*. Mount Kisco, New York: Futura Publishing Company, 1992:690, $98.00.

High-resolution electrocardiography (HRE) is a technique that allows detection and analysis of low-amplitude electrocardiographic signals that may not be detected on the body surface by routine measurements. The term "signal-energized electrocardiogram," which is frequently used synonymously with HRE, refers to 1 signal processing technique that enhances the detection of low-amplitude electrocardiographic signals. HRE began in the 1970s and the goal was to record the His-Purkinje signal noninvasively. In the mid-1970s, El-Sherif and associates observed that low-amplitude "fractionated" diastolic potentials—later called "late potentials"—are a potential marker for the anatomic electrophysiologic substrate of recurrent arrhythmias. This book provides a state-of-the art review of HRE.

30. Lüderitz B, Saksena S, editors. *Interventional*

Electrophysiology. Mount Kisco, New York: Futura, 1991:571, $95.00.

A good book.

INTERVENTIONAL CARDIOLOGY

31. Kulick DL, Rahimtoola SH, editors. *Techniques and Applications in Interventional Cardiology*. St. Louis: Mosby Year Book, 1991:527, $62.00.

32. White CJ, Ramee SR, editors. *Interventional Cardiology. Clinical Application of New Technologies*. New York: Raven Press, 1991:252, $75.00.

The Kulick-Rahimtoola book is a comprehensive, edited book divided into 4 parts: 10 chapters on intracoronary and peripheral vascular interventions; 3, on catheter valvuloplasty and dilatation of congenitally stenotic lesions; 5, on pacemakers, antitachycardia pacing, automatic implantable cardioverting and defibrillating devices, catheter ablation for tachyarrhythmias and transcoronary ablation of arrhythmogenic areas or pathways; and 2 on endomyocardial biopsy and pericardiocentesis. A fine book.

The White-Ramee book has 52% fewer pages and it costs 17% more. No comparison.

33. Clark DA. *Coronary Angioplasty*. Second Edition. New York: Wiley-Liss, 1991:302, $69.00 (with 5-hour videos, $495.00).

A fine book but the printer did not do justice to the many pictures. The price is very reasonable. Dr. Clark wrote 9 of the 13 chapters.

34. Black AJR, Anderson HV, Ellis SG, editors. *Complications of Coronary Angioplasty*. New York: Marcel Dekker, Inc., 1991:261, $99.75.

Of the many books on coronary angioplasty, relatively little attention has been given to its complications. This book is devoted exclusively to them and as such it is useful.

35. Shawl FA, editor. *Supported Complex and High Risk Coronary Angioplasty*. Boston: Kluwer Academic Publishers, 1991:261, $97.50.

Dr. Shawl has been a leader in the clinical application of percutaneous cardiopulmonary bypass support techniques, and this edited book provides to the interventionist the basic principles of cardiopulmonary bypass and other alternate support devices for myocardial protection. Dr. Shawl is joined by 15 other contributors, also leaders in this field.

36. Holmes DR Jr, Garratt KN, editors. *Atherectomy*. Boston: Blackwell Scientific Publications, 1992: 230, $59.95.

Twenty-two leaders in this field author this book that probably is the best so far on this subject.

37. Karsh KR, Haase KK, editors. *Coronary Laser Angioplasty. An Update*. New York: Springer-Verlag, 1991:178, $49.00.

This book focuses exclusively on laser techniques in coronary artery stenosis, and for those still interested it would be useful.

VALVULAR HEART DISEASE

38. Emery RW, Arom KV, editors. *The Aortic Valve*. Philadelphia: Hanley & Belfus, Inc. (St. Louis: Mosby Year Book), 1991:336, $65.00.

This book is edited by 2 cardiovascular surgeons. It is well done and I highly recommend it.

39. Bodnar E, Frater R, editors. *Replacement Cardiac Valves*. New York: Pergamon Press, 1991:482, $94.50.

This multiauthored book may be the best of the more recent books on this subject. It is very comprehensive.

40. Bashore TM, Davidson CJ, editors. *Percutaneous Balloon Valvuloplasty and Related Techniques*. Baltimore: Williams & Wilkins, 1991:351, $62.00.

Surely this book is the best one on this subject. Of the 19 chapters by the 29 contributors, 15 focus on the mitral and aortic valves.

ANNUAL CARDIOLOGY REVIEWS

41. Schlant RC (editor in chief), Collins JJ Jr, Engle MA, Frye RL, Kaplan NM, O'Rourke RA (editors). *1991 The Year Book of Cardiology*. St. Louis: Mosby Year Book, 1991:379, $57.95.

42. Roberts WC (editor), Willerson JT, Mason DT, Rackley CE, Graham TP Jr. *Cardiology 1991*. Boston: Butterworth-Heinemann, 1991:494, $80.00.

The Schlant book is the thirty-first in the series. It contains summaries and comments on 305 clinically relevant articles. The Roberts book is the eleventh in the series beginning in 1981. A total of 804 articles are summarized and all articles had appeared in 1990. Additionally, the book contains 120 figures and 61 tables. Each page is fully packed. Although obviously biased I prefer the Roberts book, which summarizes 63% more articles and costs only 28% more than the Schlant book.

MISCELLANEOUS

43. Fowler NO. *Diagnosis of Heart Disease*. New York: Springer-Verlag, 1991:429, $79.00.

It is nice to see a single-authored book. This one by a masterful clinician is a good one, too.

44. Perloff JK, Child JS, editors. *Congenital Heart Disease in Adults*. Philadelphia: WB Saunders, 1991: 342, $75.00.

I was fortunate to have edited in 1979 a book entitled *Congenital Heart Disease in Adults* and a new version in 1987 entitled *Adult Congenital Heart Disease*. Thus, I feel comfortable in evaluating the new book by Drs. Perloff and Child with 19 contributors, 14 of whom are at UCLA with the 2 editors. Dr. Perloff is the author or coauthor of 17 of the book's 20 chapters. This book is unique among textbooks on congenital heart disease in that it does not focus on the specific varieties of congenital anomalies, but rather on general concepts and problems in adults. For physicians seeing adults with congenital heart disease, this is the book to have.

45. Opie LH. *The Heart. Physiology and Metabolism*. Second Edition. New York: Raven Press, 1991:513, $72.00.

A single-authored book on the fundamentals of cardiac cellular physiology.

46. Wilcox BR, Anderson RH. *Surgical Anatomy of the Heart*. Second Edition. London: Gower Medical Publishing, 1992: approximately 120 pages, $125.00.

Dr. David C. Sabiston, Jr. states in the foreword: "The second edition embraces all the excellence of its predeces-

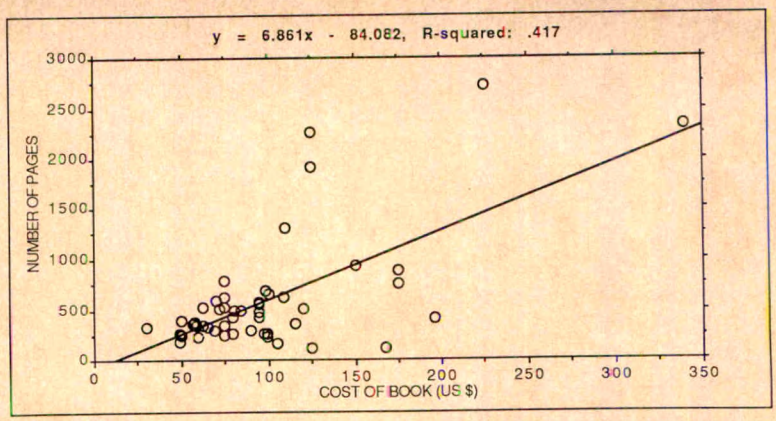


FIGURE 1. Diagram showing relation of number of pages in the 49 books to their cost.

sor and in addition contains new data on the previous subjects as well as the addition of detailed anatomy of the tricuspid, pulmonary, mitral and aortic valves and much new material on the surgical anatomy of the coronary circulation." The illustrations in this book are truly magnificent. I believe that Dr. Wilcox gets the best photographs in the operating room of any surgeon.

47. Kapoor AS, Laks H, Schroeder JS, Yacoub MH, editors. *Cardiomyopathies and Heart-Lung Transplantation.* New York: McGraw-Hill, 1991:511, $120.00.

This book provides up-to-date comprehensive coverage of developments in cardiomyopathies, cardiac assist devices and heart-lung transplantation. A fine book by 61 contributors.

48. O'Rourke MF, Kelly RP, Avolio AP. *The Arterial Pulse.* Philadelphia: Lea & Febiger, 1992:239, $49.95.

It's all here on this single topic.

49. Meester GT, Pinciroli F, editors. *Databases For Cardiology.* Dordrecht, the Netherlands: Kluwer Academic Publishers, 1991:418, $196.00.

The editors, 1 a cardiologist and 1 an information scientist, have provided "an extensive overview of the medical cardiological database field, with examples of design, construction and data-analysis, while not omitting possible problems and pitfalls."

COMMENTS

Of the 49 books reviewed here, 36 (73%) contained a 1991 publication date and 13 (27%), a 1992 publication date. The numbers of pages in these 49 books ranged from 120 to 2720 (mean 600), and the costs of the books ranged from $29.95 to $340.00 (mean $100.00). There was no relation between the number of pages a book contained and its cost (Figure 1) ($r = .42$, $p = 0.1$). Thirty-seven books (76%) were multiauthored (>10) and 12 (24%) had ≤6 authors; only 2 books had a single author.

Most books unfortunately continue to be published on acid paper.[1] Of the 49 books, only 11 (22%) (numbers 14, 15, 17, 19, 25, 27, 34, 37, 42, 43 and 49) were stated to have been published on acid-free paper, but only 1 (number 42) of them contained the permanent-paper insignia (infinity symbol within a circle) on the verso of the title page of the book indicating that the paper used was alkaline (i.e., permanent). None of the books published by American publishers were on acid-free paper! In contrast, all books published by Butterworth-Heinemann, Elsevier, Kluwen Academic, Marcel Dekker, and Springer-Verlag were on permanent (acid-free) paper. I encourage all authors to require in their book contracts that the paper used for their books be acid-free!

William C. Roberts

William Clifford Roberts, MD
Editor in Chief

1. Roberts WC. Alkaline paper and preserving the record. *Am J Cardiol* 1991;68:1729–1732.

The American Journal of Cardiology®

JANUARY 15, 1992

145 Coronary Artery Disease
201 Arrhythmias and Conduction Disturbances
213 Systemic Hypertension
233 Valvular Heart Disease
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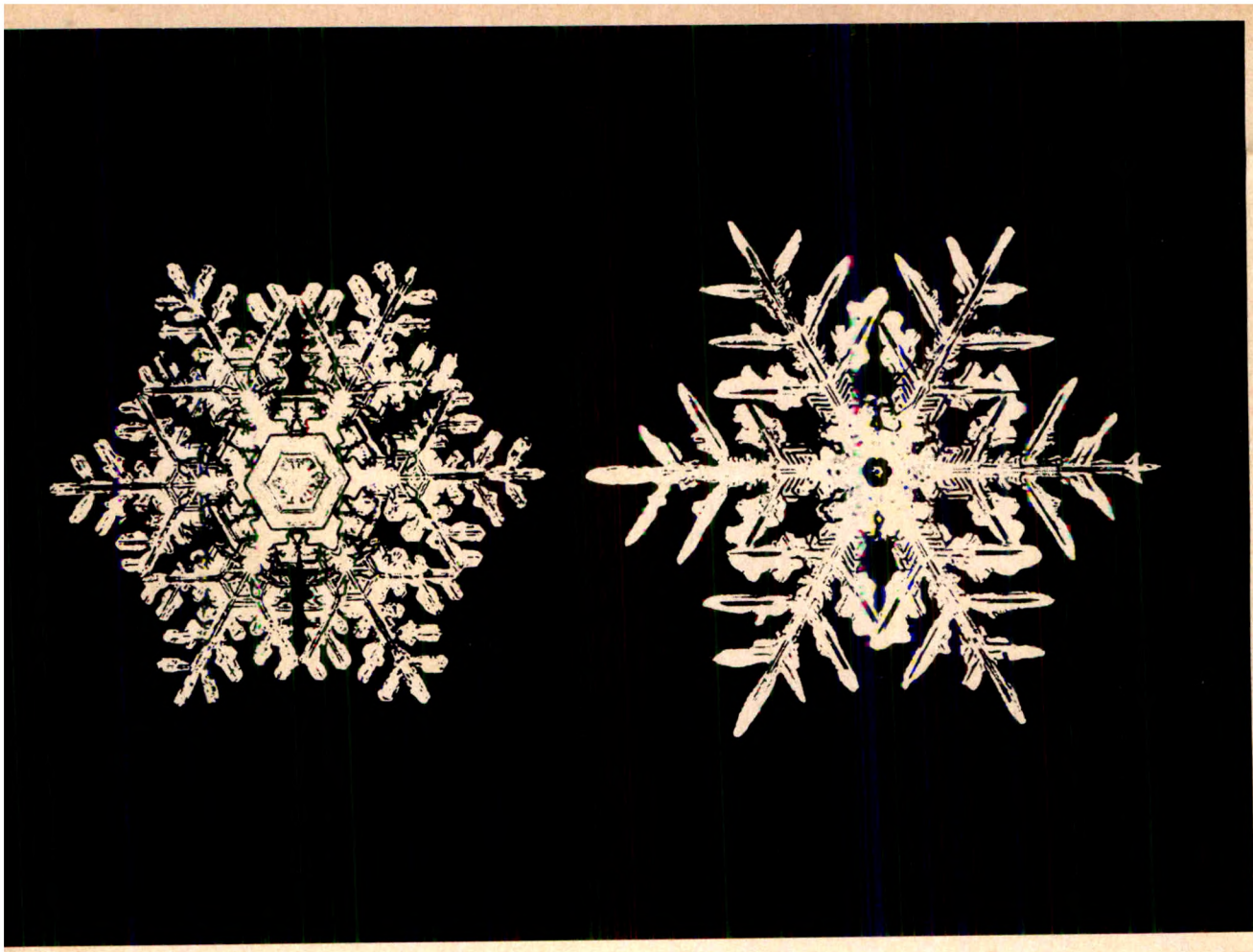
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CORONARY ARTERY DISEASE

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Long-Term Survival of Emergency Department Patients with Acute Chest Pain

Thomas H. Lee, Henry H. Ting, Jonathan B. Shammash, Jane R. Soukup, and Lee Goldman

To evaluate the long-term prognosis of emergency department patients with acute chest pain, long-term survival data were analyzed for 1,956 patients who presented to the emergency department with acute chest pain. No differences were detected in the postdischarge cardiovascular survival rates after 3 years of experience with patients who were discharged from the emergency department with a known prior history of angina or myocardial infarction (89%) and patients who had been admitted and found to have acute myocardial infarction (85%), angina (87%) or other cardiovascular diagnoses (87%). Patients who were discharged from either the hospital or the emergency department without cardiovascular diagnoses had an excellent prognosis. Multivariate Cox regression analysis identified 5 independent correlates of cardiovascular mortality after discharge: age, prior history of coronary disease, ischemic changes on the emergency department electrocardiogram, congestive heart failure and cardiogenic shock.

152
Holter Recording of Ventricular Arrhythmias During Intravenous Thrombolysis for Acute Myocardial Infarction

Virginie Gressin, Yves Louvard, Michel Pezzano, and Hervé Lardoux

Holter monitoring, began during thrombolytic therapy, and was used to describe ventricular arrhythmias and assess their relation to coronary artery patency in 40 patients with acute myocardial infarction. Artery patency was assessed by angiography (delay from pain 26.7 ± 2.5 hours). There was no difference in incidence of accelerated idioventricular rhythm and ventricular tachycardia (VT) between the patent and nonpatent groups. Sustained VT occurred only in the patent group (38 vs 0%; $p < 0.05$). The incidence of early accelerated idioventricular rhythm (before the first 6 hours) was higher in the patent group (76 vs 18%; $p < 0.01$). Coronary patency was associated with a 14-, 13- and 32-fold increase of ventricular premature complexes, VT and accelerated idioventricular rhythms, respectively. Sustained VT and early accelerated idioventricular rhythm may be considered as noninvasive criteria for reperfusion. A

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positive correlation was found between the frequency of ventricular premature complexes, VT and peak creatine kinase.

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Psychosocial Adjustment of Patients Arriving Early at the Emergency Department After Acute Myocardial Infarction

Robert M. Carney, Kenneth E. Freedland, Karen A. Clark, Judith A. Skala, Laurie J. Smith, Alan Delamater, and Allan S. Jaffe

Thrombolytic agents improve survival in patients with an acute myocardial infarction if they are administered within a few hours of onset. The psychosocial functioning of patients arriving at the emergency department early enough to be candidates for treatment with thrombolytic agents was compared with that of those arriving later. Patients who arrived within 3 hours were significantly more anxious when assessed 1 week after admission and had a consistently worse pattern of psychosocial adjustment 3 months after hospital discharge than did those who arrived later. The implications of these findings for efforts to improve early arrival at the emergency department, as well as for medical and psychosocial outcomes after acute myocardial infarction, were considered.

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Effect of Timolol on Cardiopulmonary Exercise Performance in Men After Myocardial Infarction

Ståle Barvik, Kenneth Dickstein, Torbjørn Aarsland and Harald Vik-Mo

The effect of the nonselective β blocker timolol on maximal cardiopulmonary exercise performance was evaluated in 28 men with previous myocardial infarction without effort angina. Patients were randomized to placebo or timolol for 4 weeks and then crossed over to the alternative therapy in a double-blind manner. At the completion of each treatment period, patients underwent symptom-limited maximal exercise on a cycle ergometer, and gas exchange data were collected on a breath-by-breath basis. Parameters were calculated at peak exercise and at a submaximal exercise level defined at a respiratory exchange ratio of 1.00. Oxygen consumption decreased by 15% ($p < 0.001$) at peak exercise and by 10% ($p < 0.001$) at submaximal exercise. Results indicate that use of β blockade for secondary prophylaxis substantially compromises functional capacity at peak and submaximal exercise.

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Effects of Acute K-Strophantidin Administration on Left Ventricular Relaxation and Filling Phase in Coronary Artery Disease

Roberto Bolognesi, Francesco Cucchini, Antonio Javernaro, Roberto Zeppellini, Carlo Manca, and Odoardo Visioli

The effects of an acute k-strophantidin administration on selected parameters of both left ventricular systolic (positive dP/dt, dP/dt/P, end-systolic and stroke volumes, and ejection fraction) and diastolic (negative dP/dt, T constant, minimal and end-diastolic pressures and volumes, maximal rate of volumetric increase during early and late filling phases)

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In hypertension, CAPOTEN may be used as initial therapy (25 mg bid or tid) for patients with normal renal function, in whom the risk of neutropenia/agranulocytosis is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, captopril should be reserved for hypertensives who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to drug combinations.

In heart failure, CAPOTEN should generally be added to diuretics and digitalis except when digitalis use is poorly tolerated or otherwise not feasible; add CAPOTEN when patients have not responded adequately.

CAPOTEN is contraindicated in patients who are hypersensitive to this product. Angioedema has been reported in patients receiving ACE inhibitors.

Please see INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary on the adjacent page.

functions were evaluated in 10 patients with coronary artery disease using cardiac catheterization at controlled heart rates. K-strophantidin significantly increased positive dP/dt, dP/dt/P, T constant, and lowest and end-diastolic pressures, whereas it did not change the volumetric variables. These data suggest that in patients with coronary artery disease, an acute administration of k-strophantidin may simultaneously stimulate contractility, and worsen relaxation and lowest LV and end-diastolic pressures.

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Tissue Plasminogen Activator Using a Rapid-Infusion Low-Dose Regimen for Unstable Angina

Hemant Chaudhary, Ian Crozier, Andrew Hamer, Stephan Foy, Teresa Shirlaw, and Hamid Ikram

Fifty patients with unstable angina pectoris taking aspirin, subcutaneous heparin and maximally tolerated conventional medical therapy were randomly assigned to blinded treatment with either placebo (n = 24) or low-dose (20 mg bolus, 30 mg infusion over 1 hour) intravenous recombinant tissue-type plasminogen activator (rt-PA) (n = 26). The outcome was successful (angina settled, no myocardial infarction or urgent angiography) in 15 (58%) patients from the active group and in 9 (38%) from the placebo group (p = not significant). Administration of low-dose rt-PA was not associated with any complications. Low-dose rt-PA administration in patients with unstable angina was associated with a tendency to stabilization of anginal symptoms and reduced need for urgent intervention. However, these trends did not achieve statistical significance.

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Effects of Estrogen Replacement Therapy on Serum Lipid Values and Angiographically Defined Coronary Artery Disease in Postmenopausal Women

Mun K. Hong, Philip A. Romm, Kathleen Reagan, Curtis E. Green, and Charles E. Rackley

The effect of estrogen replacement therapy on lipids and angiographic coronary artery disease (CAD) was studied in 90 consecutive postmenopausal women undergoing diagnostic coronary angiography (18 [20%] were receiving estrogen, and 72 [80%] were not). CAD (defined as ≥25% narrowing in a coronary artery) was present in 22% of women (4 of 18) receiving estrogen and in 68% (49 of 72) who were not ($p < 0.001$), with an odds ratio of 0.13. Mean high-density lipoprotein (HDL) cholesterol level was significantly higher (63 vs 48; $p < 0.01$) and mean total/HDL cholesterol ratio significantly lower in women on estrogen (4.2 vs 5.1; $p < 0.05$). On multivariate analysis, absence of estrogen use was the most powerful independent predictor of the presence of CAD ($p < 0.001$), with total/HDL cholesterol ratio as the only other variable selected ($p < 0.01$). Thus, in these women, estrogen therapy was associated with an 87% reduction in angiographic CAD, and with a significantly higher mean HDL cholesterol level and lower mean total/HDL cholesterol ratio.

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Patterns of Referral and Recovery in Women and Men Undergoing Coronary Artery Bypass Grafting
Kathleen B. King, Patricia C. Clark, and George L. Hicks, Jr.

Factors before and after coronary surgery were examined in 465 women and 465 men matched for age who underwent coronary artery surgery. Women had a higher incidence of cardiac-related risk factors than did men and were more likely to undergo emergency surgery. The in-hospital death rate was not different (women 4.3% vs men 3.7%). For all subjects, emergency surgery, left main narrowing and renal disease were related to death, whereas history of myocardial infarction and diabetes were related to death only in men. The data suggest that women and men do not share all the same predictors of mortality after surgery.

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Comparison Between Thallium-201 and Technetium-99m Methoxyisobutyl Isonitrile Defect Size in Single-Photon Emission Computed Tomography at Rest, Exercise and Redistribution in Coronary Artery Disease
Jean C. Maublant, Xavier Marcaggi, Jean-René Lusson, Jean-Yves Boire, Jean-Christophe Cauvin, Pierre Jacob, Annie Veyre, and Jean Cassagnes

Defect size, expressed in percentage of the volume of left ventricular myocardium, was measured on tomograms obtained with thallium-201 (Tl-201) and technetium-99m methoxyisobutyl isonitrile (MIBI) in 15 patients with myocardial infarction at rest, and in 15 patients with coronary artery disease at peak exercise. There was no significant difference in the group with myocardial infarction (11.2 ± 10.4% with Tl-201 and 12.0 ± 11.5% with MIBI), whereas in the group with coronary artery disease, defect size was significantly larger with Tl-201 than with MIBI (6.7 ± 5.2 and 4.6 ± 5.2%, respectively, $p < 0.05$). Correlation between the 2 agents was also weaker at exercise ($r = 0.76$) than at rest ($r = 0.96$).

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Effectiveness of Decremental Diameter Balloon Catheters (Tapered Balloon)
Vidya S. Banka, Howard A. Baker III, Dwarka N. Vemuri, Gerardo Voci, and Alan R. Maniet

To determine the natural tapering of coronary arteries and to demonstrate the need for a new decremental diameter angioplasty balloon, 100 consecutive coronary arteries were analyzed by videodensitometry. In 42% of the coronary arteries there was >0.5 mm tapering of the artery when measured 1 cm proximal and distal to the stenosis. To avoid balloon size mismatch in tapered arteries ($n = 94$), 2 sizes of tapered balloons (25 mm length) were developed: series I tapered from 3.5 to 3.0 mm, and series II from 3.0 to 2.5 mm. Artery diameter measurements before percutaneous transluminal coronary angioplasty were: proximal 3.6 ± 0.6 mm, stenotic 1.1 ± 0.5 mm, and distal 2.6 ± 0.7 mm; after percutaneous transluminal coronary angioplasty diameters were: proximal 3.6 ± 0.7 mm, stenotic 2.8 ± 0.7 mm, and distal 2.5 ± 0.6 mm, maintaining a natural taper. Only 2 (2.1%) arteries showed dissection with no abrupt occlusion or need for

Continued on page A29

coronary artery bypass graft. Decremental diameter balloon catheters offer a new approach to balloon sizing in tapered arteries minimizing the risk of dissection.

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Postangioplasty Restenosis Rate Between Segments of the Major Coronary Arteries

Walter R. M. Hermans, Benno J. Rensing, Johannes C. Kelder, Pim J. de Feyter, and Patrick W. Serruys

Conflicting data have been published regarding the rate of postangioplasty restenosis between coronary arteries after successful percutaneous transluminal coronary angioplasty. In this study, 1,353 patients underwent a successful percutaneous transluminal coronary angioplasty of ≥1 site. In all, 1,234 patients (91%) had a follow-up angiogram after 6 months, or earlier when indicated for symptoms. All films were processed and analyzed at the thoraxcenter core laboratory with the coronary angiography analysis system (automated contour detection). No differences in restenosis rates (defined as >50% diameter stenosis at follow-up) were observed between the coronary segments. A continuous approach was used to compare vessels of different sizes (relative loss, defined as the decrease in minimal luminal diameter during follow-up, normalized for the reference diameter), and here also, no differences were observed. Restenosis is a ubiquitous phenomenon without any predilection for a particular site in the coronary tree.

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Spectral Analysis of Heart Rate Dynamics in Elderly Persons with Postprandial Hypotension

Sheila M. Ryan, Ary L. Goldberger, Robin Ruthazer, Joseph Mietus, and Lewis A. Lipsitz

Autonomic control of heart rate (HR) was examined after a meal using spectral analysis of HR data in 13 elderly subjects with postprandial hypotension and 7 healthy young subjects. Mean change in total- and low-frequency HR power from 30 to 50 minutes after the meal was significantly greater in young versus old subjects. The increase in low-frequency power in the young is consistent with sympathetic activation after a meal. Absence of this finding in the elderly with postprandial hypotension suggests defective baroreflex compensation for the hypotensive effects of a meal in these subjects.

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Pharmacology of the Class III Antiarrhythmic Agent Sematilide in Patients with Arrhythmias

Wilson Wong, Harris N. Pavlou, Ulrika M. Birgersdotter, Daniel E. Hilleman, Syed M. Mohiuddin, and Dan M. Roden

Sematilide prolongs cardiac action potentials in vitro without depressing maximum action potential upstroke slope, a "class III" action. In this

dose-ranging, placebo-controlled evaluation of intravenous sematilide in 14 patients with chronic high-frequency nonsustained ventricular arrhythmias, QTc was prolonged in a dose- and concentration-related fashion ($r = 0.66$ to 0.92; $p < 0.001$), PR and QRS were unchanged, and heart rate was slowed at high concentrations. The elimination half-life was 3.6 ± 0.8 hours, and 77 ± 13% of a dose was recovered unchanged in urine. Arrhythmia suppression was seen in 5 patients and aggravation in 3, including 1 torsades de pointes. Thus, sematilide exerts class III electrophysiologic actions in patients.

SYSTEMIC HYPERTENSION

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Epidemiologic Aspects of Isolated Systolic Hypertension and Implications for Future Research

Christopher A. Silagy and John J. McNeil

Isolated systolic hypertension remains a significant public health issue in the 1990s because of its high prevalence among older persons and its importance as a risk factor for cardiovascular morbidity and mortality. Recent data indicate a benefit from intervention with antihypertensive therapy. Further studies are required to elucidate the relative effectiveness of different treatment regimens. This study explores methodologic differences that may account for wide variations in prevalence rates.

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Morphologic, Hemodynamic and Coronary Perfusion Characteristics in Severe Left Ventricular Hypertrophy Secondary to Systemic Hypertension and Evidence for Nonatherosclerotic Myocardial Ischemia

Jan Laws Houghton, Albert A. Carr, L. Michael Prisant, Ward B. Rogers, Thomas W. von Dohlen, Nancy C. Flowers, and Martin J. Frank

The purpose of this study was to characterize typical cardiac and coronary artery findings in hypertensive patients with severe left ventricular (LV) hypertrophy but without significant obstructive coronary artery disease and to investigate the evidence for myocardial ischemia in early and advanced hypertensive heart disease. Of 100 patients without coronary artery atherosclerosis who underwent cardiac catheterization with coronary vasodilator reserve testing, 2-dimensional echocardiography and dipyridamole limited-stress thallium testing, 15 had severe hypertensive LV hypertrophy and were compared with 12 normotensive and 34 hypertensive patients without LV hypertrophy. Characteristics more often associated with severe LV hypertrophy were black race, diabetes mellitus, proteinuria, elevated serum creatinine, abnormal baseline electrocardiography, abnormal dipyridamole limited-stress thallium tests, depressed LV ejection fraction, elevated basal coronary blood flow velocity and depressed coronary vasodilator reserve. The prevalent findings of noninvasive and invasive markers for ischemia support the concept of nonatherosclerotic myocardial ischemia in this group.

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Impact of Left Ventricular Hypertrophy on Blood Pressure Responses to Exercise

David H. G. Smith, Joel M. Neutel, William F. Graettinger, Jonathan Myers, Victor F. Froelicher, and Michael A. Weber

The relation between maximal exercise blood pressure (BP) and left ventricular (LV) hypertrophy was examined in 35 normal male volunteers and 65 untreated hypertensive male patients. Contrary to previous reports, exaggerated exercise BP was not associated with LV hypertrophy in hypertensive or normotensive patients. Hypertensive patients with LV hypertrophy had the smallest increases in systolic BP with exercise and exhibited an inverse relationship between LV muscle mass and maximal exercise systolic BP ($r = -0.34$; $p = 0.005$). When compared with normotensive subjects, hypertensive patients had lower measures of maximal oxygen uptake and exercise heart rates ($p = 0.01$). This may suggest lower cardiac performance at maximal exercise and raises the possibility that hypertensive patients may have a limited ability to exhibit a full, hemodynamic response to maximal treadmill exercise. This appears most marked when hypertension and LV hypertrophy coexist.

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Hemodynamic and Metabolic Effects of Intravenous Clentiazem in Hypertensive Patients

Edward D. Frohlich, Mario McLoughlin, and Reinhard Ketelhut

Hemodynamic and metabolic effects of clentiazem, a diltiazem congener, were studied in 10 untreated essential hypertensive patients by administration of 3 intravenous doses totaling 1.0 mg/kg. Mean arterial pressure and total peripheral resistance declined from 121 ± 3 mm Hg and 47 ± 2 U (mean ± 1 SEM) to 110 ± 3 mm Hg and 33 ± 1 μ, respectively ($p < 0.05$). Cardiac output increased due to elevated cardiopulmonary volume ($p < 0.05$), peripheral venoconstriction and norepinephrine release. There was an immediate and significant reduction in plasma aldosterone; serum potassium and calcium concentrations decreased associated with a twofold increase in epinephrine ($p < 0.002$). Previous diltiazem studies, conducted similarly, did not show these changes. Therefore, clentiazem reduced mean arterial pressure through a decrease in total peripheral resistance and released epinephrine was associated with intracellular potassium influx, while inhibited aldosterone release was not compensated by altered renal blood flow, glomerular filtration or increased plasma renin activity. These findings provide further evidence that calcium antagonists are a remarkably heterogeneous group of agents.

VALVULAR HEART DISEASE

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Left Ventricular Ejection Performance in Mitral Stenosis, and Effects of Successful Percutaneous Transvenous Mitral Commissurotomy

Shinya Goto, Shunnosuke Handa, Makoto Akaishi, Sumihisa Abe, and Satoshi Ogawa

To ascertain whether ejection performance would improve with sufficient diastolic blood filling, fifteen patients with tight mitral stenosis who underwent successful percutaneous transvenous mitral commissurotomy were studied. Angiographic indexes of preload (LV end-diastolic volume) and ejection (stroke volume, ejection fraction, and mean systolic and mean normalized ejection rates) were calculated before and immediately after mitral commissurotomy. Improved blood filling (the result of successful mitral commissurotomy) produced an increase in end-diastolic volume. All 4 indexes of ejection performance also improved after mitral commissurotomy. There was good correlation between end-diastolic and stroke volumes before commissurotomy (stroke volume = 0.476 × end-diastolic volume + 16.77; r = 0.76), and the relation between them showed no change after mitral commissurotomy. It is concluded that both preload and ejection performance improved after successful mitral commissurotomy. Insufficient preload could affect ejection performance in mitral stenosis.

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Findings on Doppler Echocardiography in Asymptomatic Intravenous Heroin Users

Guillem Pons-Lladó, Francesc Carreras, Xavier Borrás, Josep Cadafalch, Montserrat Fuster, Josep Guardia, and Miquel Casas

A Doppler echocardiographic study was performed in a series of 71 active intravenous heroin consumers without a history of previous endocarditis. The purpose of the examination was the detection of morphologic or functional cardiac abnormalities induced by the drug habit. A control group of 41 normal nonaddicted subjects was also studied for comparison. No significant differences were observed between study and control groups in size of the heart chambers or in systolic and diastolic left ventricular function. A significantly higher incidence of valvular abnormalities (focal thickening or valve prolapse) was found in drug addicts ($p = 0.0009$) at the level of mitral and tricuspid valves, as was valvular regurgitation detected by Doppler ($p = 0.04$).

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CARDIOMYOPATHY

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Differences in Myocardial Fluoro-18 2-Deoxyglucose Uptake in Young Versus Older Patients with Hypertrophic Cardiomyopathy

Yutaka Kagaya, Nobumasa Ishide, Daiya Takeyama, Yuka Kanno, Yuriko Yamane, Kunio Shirato, Yukio Maruyama, Masatoshi Itoh, Tatsuo Ido, Taiju Matsuzawa, and Tamotsu Takishima

To investigate whether regional myocardial glucose use differs between patients diagnosed as having hypertrophic cardiomyopathy at a younger age and those diagnosed at middle to old age, 16 patients (group 1 aged <40; group 2 aged >40) were studied using positron emission tomography and fluoro-18 2-deoxyglucose (FDG). Percent left ventricular FDG fractional uptake did not differ between the 2 groups. Percent interregional coefficient of variation in FDG fractional uptake was increased in group 1 compared with that in group 2. Interventricular septum/left ventricular posterior wall thickness ratio and total counts in a cross-sectional image did not differ between the 2 groups. The data suggest that patients diagnosed at a younger age have more nonhomogeneous myocardial metabolic characteristics than do those diagnosed at middle to old age.

MISCELLANEOUS

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Cholinergic Baroreflex Vasodilatation: Defect in Heart Transplant Recipients Due to Denervation of the Ventricular Baroreceptor

Wolfgang von Scheidt, Michael Böhm, Brigitte Schneider, Gernot Autenrieth, and Erland Erdmann

Afferent denervation of the ventricular baroreceptor may impair reflex vasodilatation after heart transplantation and alter the regulation of blood pressure. Baroreceptor loading was performed using angiotensin II infusion in 23 heart transplant recipients with cyclosporine A immunosuppression and in 11 control subjects. After m-cholinoceptor blockade, the procedure was repeated in order to study the contribution of cholinergic effects on vasodilatation. Instantaneous vascular resistance was calculated as the ratio of mean blood pressure to stroke volume. When heart transplant recipients were compared with controls, infusion of 30 ng/kg · min of angiotensin II resulted in a significantly higher increase in mean blood pressure and instantaneous resistance. Atropine (0.015 mg/kg) did not produce any change in blood pressure or resistance response to angiotensin II in heart transplant recipients, but blood pressure and resistance response to angiotensin II increased significantly in control subjects, which was similar to the response in heart transplant recipients to angiotensin II alone. Thus, in humans, a potent cholinergic vasodilator baroreflex is present, originating exclusively from the ventricular baroreceptor. Cholinergic vasodilatation is absent after heart transplantation because of ventricular denervation.

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Evaluation of Changes in Standard Electrocardiographic QRS Waveforms Recorded from Activity-Compatible Proximal Limb Lead Positions
Olle Pahlm, Wesley K. Haisty, Jr., Lars Edenbrandt, Nancy B. Wagner, Dorina C. Sevilla, Ronald H. Selvester, and Galen S. Wagner

Proximal limb lead positions are currently used for activity-compatible electrocardiographic monitoring of myocardial ischemia. Two previously described systems for alternate limb lead placement were studied in patients with and without QRS evidence of healed anterior or inferior myocardial infarction. An innovative method was used to simultaneously record 6 standard and 6 modified limb leads, and 3 standard and 3 modified precordial leads on a standard digital electrocardiograph. Both alternate lead placement systems showed rightward frontal plane axis shift and diminished Q-wave durations in lead aVF compared with those of their simultaneous standard controls. Furthermore, other possible lead placement sites along each limb were explored. It is imperative that recordings from alternate sites be labeled accordingly so that their output cannot be confused with that obtained from standard sites.

CARDIOVASCULAR PHARMACOLOGY

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Rapidity and Duration of Platelet Suppression by Enteric-Coated Aspirin in Healthy Young Men
Alfredo H. Jimenez, Miguel E. Stubbs, Geoffrey H. Tofler, Kaj Winther, Gordon H. Williams, and James E. Muller

In healthy young men, (1) the rapidity of onset of inhibition of platelet aggregation and thromboxane A_2 production after 325 mg enteric-coated aspirin (enteric-coated aspirin) was chewed (n = 10), and (2) the duration of platelet inhibition after cessation of enteric-coated aspirin (325 mg) every other day for 14 days (n = 10) were investigated. When chewed, enteric-coated aspirin markedly inhibited platelet aggregation response to adenosine diphosphate and thromboxane A_2 production within 15 minutes. Complete recovery of platelet aggregation occurred in half of the subjects by day 3, and in 80% of subjects by day 4; the platelet response was not affected by exercise.

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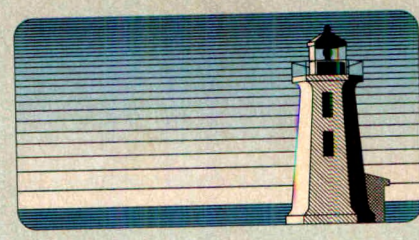
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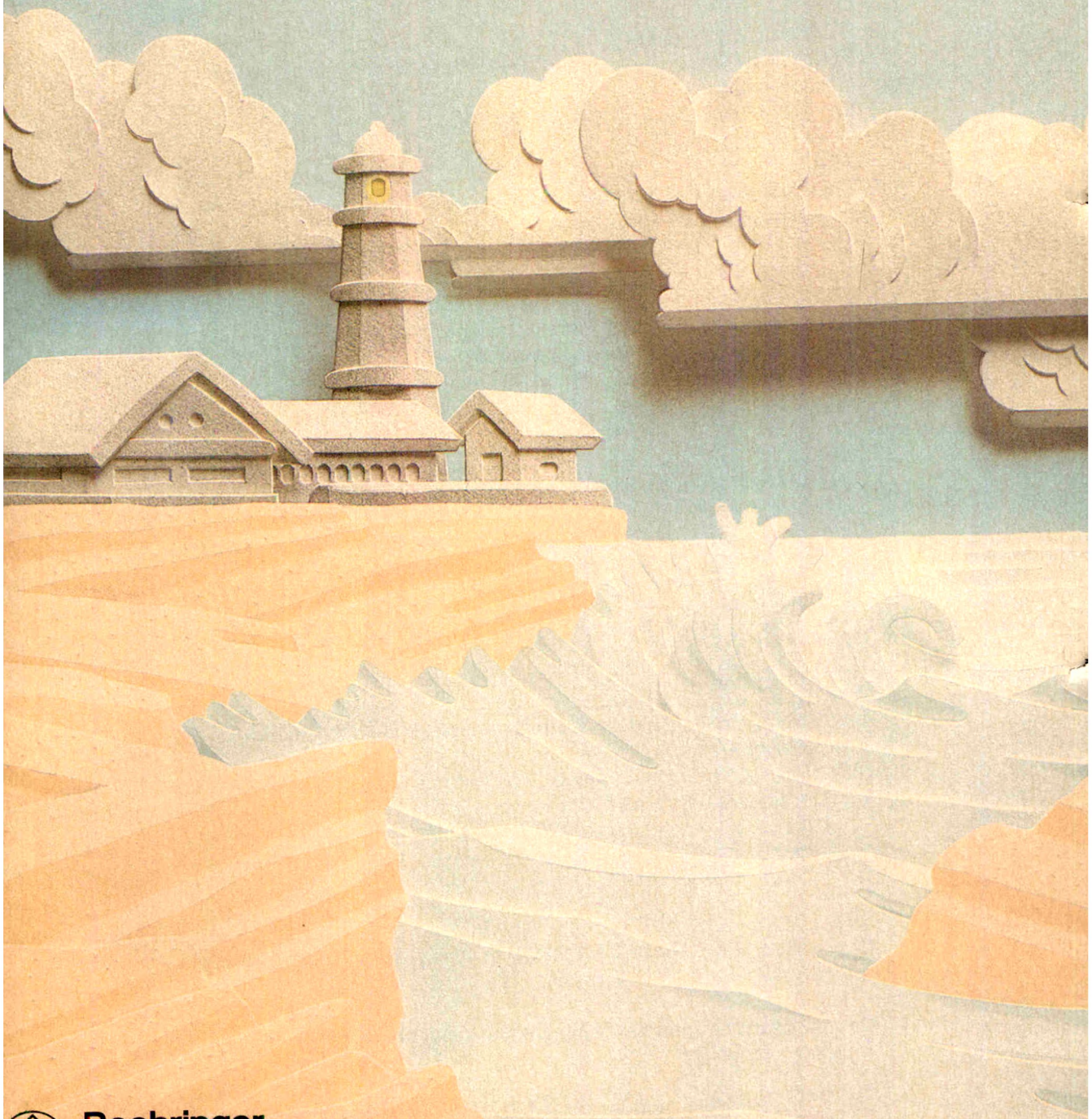
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Long-Term Survival of Emergency Department Patients with Acute Chest Pain

Thomas H. Lee, MD, Henry H. Ting, MD, Jonathan B. Shammash, BA, Jane R. Soukup, MS, and Lee Goldman, MD

To evaluate the long-term prognosis of patients with acute chest pain, prospective clinical data and long-term follow-up data (mean 30.1 ± 9.4 months) were collected for 1,956 patients who presented to the emergency department of an urban teaching hospital with this chief complaint. During follow-up of the 1,915 patients who were discharged alive from the emergency department or hospital, there were 113 (6%) cardiovascular deaths. No differences were detected in the postdischarge cardiovascular survival rates after 3 years of experience with patients who were discharged from the emergency department with a known prior diagnosis of angina or myocardial infarction (89%) and patients who had been admitted and found to have acute myocardial infarction (85%), angina (87%), or other cardiovascular diagnoses (87%). Patients who were discharged from either the hospital or the emergency department without cardiovascular diagnoses had an excellent prognosis. Multivariate Cox regression analysis identified 5 independent correlates of cardiovascular mortality after discharge: age, prior history of coronary disease, ischemic changes on the emergency department electrocardiogram, congestive heart failure and cardiogenic shock. These findings indicate that the postdischarge cardiovascular mortality of patients with chest pain who are discharged from the emergency department with a known history of coronary disease is similar to that of admitted patients with angina or myocardial infarction. These data suggest that the same types of prognostic evaluation strategies that have been developed for admitted patients with ischemic heart disease should also be considered when such patients present to the emergency department but are not admitted.

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Previous investigations have shown that patients hospitalized with acute ischemic chest pain who do not have acute myocardial infarction have a postdischarge prognosis similar to that in patients who are discharged alive after acute myocardial infarction,[1-3] suggesting that similar risk stratification and treatment strategies should be used in both populations.[1] However, these conclusions have been based on study populations ranging in size from 211 to 632 patients, and did not include patients who are discharged from the emergency department after evaluation for acute chest pain. Therefore, we studied the long-term cardiovascular and overall survival of 1,956 patients who came to the emergency department and who were evaluated for acute chest pain, including 964 patients who were admitted for further care and 992 who were discharged directly from the emergency department. These survival data have important implications for the evaluation and management of both admitted and discharged patients.

METHODS

Patient population: All patients aged ≥30 years who were evaluated in the emergency department of Brigham and Women's Hospital, Boston, Massachusetts, from January 1984 to November 1986 after presenting with a chief complaint of anterior, precordial or left-sided chest pain unexplained by obvious local trauma or abnormalities on chest roentgenograms were eligible for this investigation. This report includes data on a total of 1,956 patients, who represent 96% of the population that was eligible for the study. All 964 admitted patients were included in the study, whereas nonadmitted patients were excluded if they would not consent to return in 48 to 72 hours for measurement of cardiac enzymes and an electrocardiogram. Of the 992 patients who were sent home from the emergency department after consenting to the follow-up protocol, 608 (61%)

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actually returned for measurement of cardiac enzymes or electrocardiograms, or both. For the other 384 nonadmitted patients who were included in the study, sufficient follow-up data were available by telephone contact or from medical records for reviewers who were unaware of emergency department data to place the patient into a diagnostic category as described elsewhere.[4-17]

Data collection: Detailed clinical data from the history (including the presence or absence of any prior history of angina or myocardial infarction diagnosed before the emergency department visit), physical examination and electrocardiogram were recorded by the emergency department resident or by a research nurse on a data collection form according to the protocol of the Multicenter Chest Pain Study.[4-17] Electrocardiographic abnormalities on the emergency department tracing were considered new unless they could be confirmed as being present on prior electrocardiograms. The person who completed the form had no knowledge of, and thus could not be influenced by, the patient's course after treatment in the emergency department.

For admitted patients, detailed information on cardiac enzymes, complications, and procedures after admission was recorded by a research nurse. Nonadmitted patients who gave consent but would not return for follow-up cardiac enzymes and electrocardiograms were contacted by telephone for assessment of their clinical status. In such cases, patients who were considered at higher risk for myocardial infarction because of a suspicious pain description, electrocardiographic abnormalities or continuing symptoms were encouraged to return for evaluation. If they were still unwilling to return, further follow-up was obtained from patients by telephone or by contact with the patients' physicians.

Diagnostic criteria: Discharge diagnoses were assigned by reviewers who were blinded to the emergency department clinical data. The diagnosis of acute myocardial infarction was made if one of the following criteria was met: (1) characteristic evolution of serum enzyme levels, including a creatine kinase (CK)-MB isoenzyme detected in more than trace amounts by the qualitative electrophoretic assay or in amounts of ≥5% of the total CK level with a typical increase and decrease on the quantitative assay; (2) if the CK-MB level was not assayed, a typical increase and decrease in the total CK with a peak value at least twice the upper limit of normal; (3) a level of lactate dehydrogenase isoenzyme 1 that was greater than that of lactate dehydrogenase 2 in the absence of hemolysis or renal infarction; or (4) an electrocardiogram showing the development of new pathologic Q waves (≥0.04 second in duration) and ≥25 percent decrease in the amplitude of the following R wave, as compared with that of the electrocardiogram obtained in the emergency department. Patients who had sudden cardiac arrests within 72 hours after the emergency department evaluation were also classified as having acute myocardial infarction if they died before it was possible to obtain enzymatic confirmation of myocardial necrosis and if there were no other explanations for the arrest. In all such patients, the presenting characteristics, electrocardiograms and clinical courses were most consistent with acute myocardial infarction. Of the 170 patients with acute myocardial infarction in this population, 146 (86%) were diagnosed on the basis of elevated total CK levels and CK-MB levels that were ≥5% of the total CK concentration.

The diagnosis of angina was made if acute myocardial infarction was not diagnosed and if the diagnosis of angina was made by the senior clinician associated with the case and was not contradicted by coronary angiographic data. "Other cardiovascular diagnoses" included congestive heart failure, supraventricular or ventricular arrhythmias, or valvular heart disease.

Long-term survival data: Prospective long-term follow-up data were collected ≥12 months after the patient's emergency department visit according to 7-step protocol: (1) attempted telephone contact of the patient, (2) attempted telephone contact of the patient's next-of-kin, (3) questionnaire mailed to the patient's last known address, (4) hospital record review, (5) attempted telephone or mail contact with patient's physician, (6) review of death certificates from the Massachusetts Bureau of Vital Statistics, and (7) a national search for death certificates using the National Death Index for patients whose survival status otherwise could not be verified.

Among the 1,956 patients enrolled in the study, 1,915 patients were discharged alive from the hospital or emergency department, and 41 patients died in the hospital. Postdischarge survival status on 1,774 patients (93%) at ≥1 year after presentation to the emergency department was determined by using the follow-up protocol. The remaining 141 patients (7%) were assumed to be alive in 1988 if not listed in the National Death Index by 1990. Information on the cause of death (cardiovascular versus noncardiovascular) was taken from the primary cause of death listed on medical records, next-of-kin report and death certificates. Mean (± SD) follow-up time for the entire patient population was 30.1 ± 9.4 months.

Analysis: Patients who were discharged alive from the hospital or the emergency department were divided into 6 groups on the basis of their initial triage, discharge diagnosis and previous cardiac history. Patients discharged alive from the hospital were divided into 4 diagnostic categories, including acute myocardial infarction, angina, other cardiovascular diagnoses and noncardiovascular diagnoses. Patients discharged alive from the emergency department were divided into those with and without a prior history of coronary artery disease. Patient subsets are defined in Table I.

The Kaplan-Meier life-table method[18] was used to calculate cardiovascular survival for each of the 6 groups of patient discharged alive from the hospital or emergency department; admitted patients who did not survive the hospitalization were excluded from the analyses. In the analysis of cardiovascular survival, patients who died from noncardiac causes were considered lost to follow-up at that time. The survival curves of the 6

patient subsets were compared using the Mantel-Cox nonparametric rank test.[19]

Univariate analyses: The Kaplan-Meier life table method[18] was used to calculate cardiovascular survival rates for patient groups defined by 19 clinical, triage, hospital complication, and hospital procedure variables. The relation between each variable and cardiovascular survival was evaluated using univariate Cox regression analyses.[20] The mortality rate ratio, which represents a comparison of the unadjusted risks of cardiovascular mortality with and without the factor, was calculated for each variable.

In these analyses, patients were considered to have evidence of new ischemia or infarction on the emergency department electrocardiogram if the physician detected: (1) probable new transmural myocardial infarction with ≥1 mm ST elevation or Q waves in ≥2 leads, (2) new ischemia or strain with ≥1 mm ST depression in ≥2 leads, or (3) other new ST or T-wave changes of ischemia or strain. Congestive heart failure was diagnosed if a physician had documented clinical or radiographic features of pulmonary edema or congestion at the time of the emergency department evaluation or during the admission to the hospital.

Multivariate analysis: The independent clinical correlates of cardiovascular mortality in the patients who were discharged alive from the hospital or emergency department were evaluated in a Cox proportional hazards analysis that considered 36 variables in a step-wise fashion in the Cox regression model.[20] These variables included 30 clinical variables from the emergency department evaluation and cardiovascular complications occurring during the emergency department evaluation or during a subsequent hospitalization. Cardiovascular complications that were considered in these analyses included congestive heart failure, ventricular fibrillation, recurrent ischemic pain, infarct extension, cardiogenic shock, and detection during routine care of ≥6 ventricular premature contractions per minute.

TABLE I Patient Subsets

Group	Emergency Department Triage	Diagnosis
I	Admitted	Acute myocardial infarction
II	Admitted	Angina without infarction
III	Admitted	Other cardiovascular diagnoses
IV	Admitted	Noncardiovascular diagnoses
V	Discharged	History of coronary disease
VI	Discharged	No history of coronary disease

TABLE II One- to Three-Year Cardiovascular Survival Among 1,915 Patients with Acute Chest Pain

Group	No. of Pts.	Years of Follow-Up 1	2	3
Admitted to Hospital				
Discharge diagnosis				
I–Acute myocardial infarction	170	0.935	0.884	0.850
II–Angina	318	0.939	0.898	0.872
III–Other cardiovascular	124	0.934	0.898	0.874
IV–Noncardiovascular	311	0.981	0.974	0.958
Discharged from Emergency Department				
Prior history of coronary disease				
V–Yes	168	0.946	0.927	0.894
VI–No	824	0.995	0.989	0.985

Comparisons of Postdischarge Cardiovascular Survival Rates	
Groups	p Value
I, II, III, and V	NS
I vs IV	<0.0001
II vs IV	<0.0001
III vs IV	<0.01
V vs VI	<0.0001
IV vs VI	<0.01

NS = not significant.

RESULTS

The 1,956 patients in this report included 964 (49%) consecutive patients who were admitted to the hospital and 992 (51%) who were discharged from the emergency department. Of the 964 admitted patients, 41 (4%) did not survive hospitalization, and 923 (96%) were discharged alive from the hospital; thus, 1,915 patients were discharged alive from the hospital or emergency department. At follow-up (mean 30.1 ± 9.4 months), 189 (10%) of the 1,915 patients discharged alive had died, including 113 (6%) cardiovascular deaths.

Comparison of postdischarge cardiovascular survival among patient groups: Of the 923 patients who were admitted to the hospital and discharged alive, 612 (66%) had discharge diagnoses of acute myocardial infarction, angina or other cardiovascular diagnoses, and 311 (34%) had noncardiovascular diagnoses (Table I). Among 992 patients discharged from the emergency department, 168 (17%) had a prior history of myocardial infarction or angina.

When the cardiovascular survival rates for the patient groups determined by triage, discharge diagnosis and prior history were compared, no difference in cardiovascular survival was found among groups I, II, III and V ($p = 0.7$) (Table II). Thus, patients discharged from the emergency department who had a known history of coronary artery disease had a cardiovascular prognosis similar to that of patients discharged from the hospital with a diagnosis of acute myocardial infarction, angina, or other cardiovascular diagnoses.

Survival rates in these groups were similar even though several clinical features associated with increased risk for acute myocardial infarction were less common among patients who were discharged from the emergency department despite a known history of coronary artery disease than among patients who were discharged alive with cardiovascular diagnoses. For example, compared with patients who were admitted and ultimately discharged alive with a diagnosis of angina

TABLE III Survival in 1,915 Patients Discharged Alive from the Hospital or Emergency Department

Factor	No. (%)	Survival (years) (life-table analysis) 1	2	3	Mortality Rate Ratio (95% CI)	p Value
Age (years)						
30–39	333 (17)	0.99	0.98	0.98	—	
40–49	397 (21)	0.99	0.99	0.98	1.0 (0.6,1.8)	NS
50–59	422 (22)	0.96	0.95	0.93	4.1 (2.5,6.7)	<0.005
60–69	366 (19)	0.97	0.93	0.92	5.4 (3.3,8.3)	<0.001
≥70	397 (21)	0.94	0.89	0.84	9.2 (5.8,14.8)	<0.0001
Gender						
Men	864 (45)	0.96	0.94	0.93	1.1 (0.9,1.4)	NS
Women	1,051 (55)	0.97	0.96	0.93	—	
History of coronary artery disease						
Yes	653 (34)	0.94	0.90	0.86	4.4 (3.6,5.4)	<0.0001
No	1,262 (66)	0.99	0.98	0.96	—	
History of coronary artery bypass surgery						
Yes	130 (7)	0.93	0.84	0.82	3.3 (2.6,4.2)	<0.0001
No	1,785 (93)	0.97	0.96	0.94	—	
Emergency department EKG with changes of ischemia or infarction not known to be old*						
Yes	414 (22)	0.93	0.89	0.85	3.8 (3.1,4.6)	<0.0001
No	1,447 (78)	0.98	0.97	0.95	—	
Triage decisions						
Admitted to hospital						
Yes	923 (48)	0.95	0.92	0.89	3.8 (3.0,4.7)	<0.0001
No	992 (52)	0.99	0.98	0.97	—	
Admitted to coronary care unit						
Yes	618 (32)	0.95	0.92	0.88	2.6 (2.2,3.2)	<0.0001
No	1,297 (68)	0.98	0.97	0.95	—	
Complications						
Congestive heart failure						
Yes	155 (8)	0.89	0.82	0.75	5.1 (4.2,6.3)	<0.0001
No	1,760 (92)	0.98	0.96	0.95	—	
Ventricular fibrillation						
Yes	17 (1)	0.94	0.79	0.79	3.4 (1.5,6.2)	<0.05
No	1,898 (99)	0.97	0.95	0.93	—	
Recurrent ischemic pain						
Yes	157 (8)	0.97	0.92	0.87	2.0 (1.6,2.6)	<0.01
No	1,758 (92)	0.97	0.95	0.94	—	
Infarct extension						
Yes	10 (0.5)	0.80	0.70	0.70	5.9 (3.3,10.7)	<0.005
No	1,905 (99.5)	0.97	0.95	0.93	—	
Cardiogenic shock						
Yes	11 (0.6)	0.91	0.81	0.63	5.5 (3.0,9.8)	<0.005
No	1,904 (99.4)	0.97	0.95	0.93	—	
Ventricular premature contractions ≥ 6/min						
Yes	97 (5)	0.89	0.83	0.80	3.8 (2.9,4.9)	<0.0001
No	1,818 (95)	0.97	0.96	0.94	—	
Inpatient procedures						
Cardioversion						
Yes	17 (1)	1.00	1.00	1.00	—	NS
No	1,898 (99)	0.97	0.95	0.93	—	
Cardiac catheterization						
Yes	180 (9)	0.98	0.95	0.93	1.0 (0.7,1.4)	NS
No	1,735 (91)	0.97	0.95	0.93	—	
Coronary artery bypass surgery						
Yes	48 (2)	1.00	0.98	0.98	0.7 (0.3,1.4)	NS
No	1,867 (98)	0.97	0.95	0.93	—	
Intraaortic balloon counterpulsation						
Yes	12 (0.6)	0.92	0.73	0.73	5.1 (2.8,9.2)	<0.01
No	1,903 (99.4)	0.97	0.95	0.93	—	
Emergent endotracheal intubation						
Yes	13 (0.7)	0.85	0.66	0.66	7.0 (4.2,11.7)	<0.0005
No	1,902 (99.3)	0.97	0.95	0.93	—	
Thrombolytic therapy						
Yes	28 (2)	0.96	0.96	0.90	1.2 (0.6,2.4)	NS
No	1,887 (98)	0.97	0.95	0.93	—	

*Data on the emergency department physician's interpretation of the electrocardiogram were unavailable for 54 patients.
CI = confidence interval; EKG = electrocardiogram; NS = not significant.

(group II), patients who were discharged from the emergency department despite a history of coronary artery disease (group V) were less likely (1) to describe the quality of their chest pain as "pressure" (47 vs 77%; $p < 0.0001$); (2) to have radiation of chest pain to the neck, jaw, or left arm or shoulder (21 vs 48%; $p < 0.0001$); (3) to be diaphoretic (17 vs 36%; $p < 0.0001$) or dyspneic (33 vs 58%; $p < 0.0001$); (4) to have known coronary disease documented by a prior coronary angiography (10 vs 18%; $p < 0.05$); (5) to have rales detected during chest auscultation (16 vs 28%; $p < 0.01$); or (6) to have an electrocardiogram in the emergency department showing changes consistent with ischemia or infarction that were not known to be old (6 vs 44%; $p < 0.0001$). The discharged patients were more likely to describe their pain as pleuritic (17 vs 4%) or positional (13 vs 3%) or being reproduced by chest wall palpation (29 vs 4%) (all $p < 0.0001$).

Patients who were discharged from either the hospital or the emergency department without cardiovascular diagnoses had an excellent prognosis (Table II). Thus, hospitalized patients with noncardiovascular diagnoses (group IV) had significantly better survival than all other groups of hospitalized patients, and patients discharged from the emergency department who did not have known histories of coronary disease had a significantly better survival than discharged patients with such a prior history (group VI). Patients discharged from the emergency department without a history of coronary artery disease (group VI) also had significantly better cardiovascular survival than patients discharged from the hospital with a noncardiovascular diagnosis (group IV; $p < 0.01$).

Univariate predictors of survival: In the analyses of the univariate correlates of cardiovascular survival (Table III), several variables had significant univariate associations with cardiovascular postdischarge mortality. Factors from the emergency department evaluation that were associated with worsened survival included age, prior history of coronary artery disease or coronary artery bypass surgery, and evidence on the emergency department electrocardiogram of ischemia or infarction not known to be old. Patients also had higher cardiovascular mortality if they were admitted and had complications including congestive heart failure, ventricular fibrillation, recurrent ischemic pain, extension of infarction, cardiogenic shock, or ≥ 6 ventricular premature contractions per minute noted during routine care. Of these complications, congestive heart failure and recurrent ischemic pain were the most common. Heart failure was associated with a mortality rate ratio of 5.1 (95% confidence interval 3.4, 7.7; $p < 0.0001$).

Patients who were admitted and underwent cardioversion, cardiac catheterization, coronary artery bypass surgery or thrombolytic therapy did not have worsened survival after discharge, but cardiovascular mortality was high among the small numbers of patients who were discharged alive after undergoing intraaortic balloon counterpulsation or emergent endotracheal intubation.

TABLE IV Independent Predictors* of Long-Term Survival After Discharge from the Hospital or Emergency Department

Factor	Mortality Rate Ratio† (95% CI)	p Value
Age (10-year increment)	1.4 (1.3,1.5)	<0.0001
History of coronary artery disease	2.2 (1.7,2.7)	<0.001
Emergency department electrocardiogram with changes of ischemia or infarction not known to be old	2.1 (1.7,2.6)	<0.001
Congestive heart failure during emergency department evaluation or after admission to hospital	2.4 (1.9,3.0)	<0.001
Cardiogenic shock after admission to hospital	3.7 (2.0,6.8)	<0.05

*One hundred fifty-two of 1,915 (8%) observations deleted due to missing values.
†Rate ratios were calculated by the exponentiation of the coefficients derived from a stepwise Cox proportional hazards model.

Multivariate Cox proportional hazards analysis: In a multivariate Cox regression analysis, 5 factors were found to have independent correlations with long-term cardiovascular survival. Each 10-year increment in age was associated with a mortality rate ratio of 1.4 (Table IV). Other independent correlates included prior history of angina or myocardial infarction, evidence of ischemia or infarction not known to be old on the emergency department electrocardiogram, and the occurrence of congestive heart failure or cardiogenic shock in the emergency department or during hospitalization.

Variables that had significant univariate association with survival but were not found to be independent correlates of cardiovascular mortality included: past history of coronary artery surgery and the occurrence of ventricular fibrillation, recurrent ischemic pain, infarct extension, or ventricular premature contractions in admitted patients.

DISCUSSION

Although clinical investigations have helped define strategies for the evaluation of patients who survive acute myocardial infarction,[21] management of the far larger number of patients with acute chest pain who do not have myocardial infarction remains highly variable, reflecting uncertainty over the prognosis of patient groups within this population. Previous investigations have demonstrated that patients who are admitted to the hospital for acute chest pain who do not have acute myocardial infarction have postdischarge cardiovascular mortality rates that are as high[1-3] or nearly as high[22-24] as patients who are discharged alive after acute myocardial infarctions. However, each of these prior investigations were based on fewer than 600 patients, and none included patients with acute chest pain who were discharged from the emergency department.

The data in this report are consistent with and extend the findings of these previous investigations.

Among the 1,915 patients who were discharged alive from the hospital or emergency department, those who were discharged with acute myocardial infarction had a prognosis similar to other patients who were discharged with known cardiovascular disease, including those who were sent home directly from the emergency department. All of these patient groups had annual mortality rates that were considerably higher than the 2.1% annual mortality among patients with stable coronary disease who were randomized to medical therapy in the Coronary Artery Surgery Study.[25] This difference may reflect greater severity of coronary artery disease and other co-morbid medical conditions in this unselected population than in the persons who enrolled in the Coronary Artery Surgery Study.

These findings suggest that postdischarge noninvasive evaluation strategies for patients who "rule-in" for an acute myocardial infarction[21,26-29] should be considered for patients with acute chest pain who "rule-out" for acute myocardial infarction, including patients who are considered sufficiently stable to be discharged directly from the emergency department. Wilcox et al[30] recently reported that the results of predischarge testing added independent prognostic information to clinical data for patients with unstable angina who were discharged with medical therapy.[30] Thus, these strategies might include the use of exercise testing before discharge or shortly afterwards.

Our findings also demonstrate that clinical data can be used to stratify both admitted and discharged patients with acute chest pain. Multivariate analysis indicated that the independent predictors of postdischarge cardiovascular mortality include age, a prior history of angina or myocardial infarction, electrocardiographic evidence of ischemia, and left ventricular dysfunction as manifested by congestive heart failure or cardiogenic shock. This analysis is consistent with previous studies demonstrating the prognostic importance of electrocardiographic findings during[31] and after[24] hospitalization, and the negative impact of left ventricular dysfunction on survival.[25]

These data should be interpreted with caution, since this study is subject to certain limitations that may restrict its generalizability. The cohort in this report was assembled at a single urban teaching hospital, and patients received their subsequent care from a variety of types of health care providers. Furthermore, these patients were initially seen in 1984 to 1986, and treatment of acute myocardial infarction and unstable angina has continued to evolve in subsequent years, with more aggressive use of thrombolytic therapy, percutaneous coronary angioplasty and other therapies.

However, it is unlikely that more aggressive immediate management of acute myocardial infarction and unstable angina have altered the basic finding of this report — that postdischarge risk is similar among all groups of patients with known cardiovascular disease. These data therefore demonstrate the importance of risk stratification for patients with acute chest pain who do not have acute myocardial infarction, and support the extensions of prognostic evaluation strategies, such as exercise testing, to other patients with known or suspected coronary artery disease, including patients who are considered sufficiently stable to be discharged directly from the emergency department.

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Holter Recording of Ventricular Arrhythmias During Intravenous Thrombolysis for Acute Myocardial Infarction

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Ventricular arrhythmias during thrombolysis for acute myocardial infarction and their relation to coronary artery patency were examined. Twenty-four-hour Holter monitoring was begun 3.1 ± 0.2 hours after onset of pain in 40 patients (age 54 ± 1.6 years; anterior infarction 42.5%) treated with streptokinase (42.5%) or recombinant tissue-type plasminogen activator (57.5%) (delay from pain 3.3 ± 0.2 hours). A Marquette 8000 computer was used for Holter analysis. The infarct-related artery was considered as patent (72.5%) or nonpatent (27.5%) according to coronary angiography (delay from pain 26.7 ± 2.5 hours; 60% <24 hours). Ventricular arrhythmias were present in all patients. Tolerance was good (1 cardioversion for ventricular fibrillation). The incidence of accelerated idioventricular rhythm was not different between patients with a patent and nonpatent artery (90 vs 82%), nor for ventricular tachycardia (VT) (83 vs 73%). Coronary artery patency was associated with a 14-, 13- and 32-fold increase of ventricular premature complexes, VT and accelerated idioventricular rhythms, respectively. The increased incidence of sustained VT (patent 38%; nonpatent 0%; p <0.05) and early (before the first 6 hours) accelerated idioventricular rhythm (patent 76%; nonpatent 18%; p <0.01) associated with artery patency suggests that these arrhythmias may be noninvasive diagnostic criteria for reperfusion (sensitivity 38 vs 76%, and specificity 100 vs 82%). A positive correlation was found between the frequency of ventricular premature complexes and VT, and peak creatine kinase.

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Reperfusion arrhythmias were widely described in animal models of myocardial infarction.[1–3] They were reported to occur in humans undergoing coronary angioplasty during the acute phase of myocardial infarction. Their incidence during intravenous thrombolysis has rarely been studied using rigorous methods such as Holter recordings. The usefulness of thrombolytic therapy is now proven.[4–7] Its potential administration before admission to the hospital needs a better understanding of this "rhythmic risk." We performed a prospective study in patients treated with intravenous thrombolytic therapy for acute myocardial infarction, the objectives of which were to identify ventricular arrhythmias occurring within the first 24 hours using 24-hour Holter recordings and to analyze the incidence and frequency of ventricular arrhythmias according to the patency of the infarct-related artery as assessed by coronary angiography performed within 72 hours of onset of pain.

METHODS

Study patients: From April 1987 to November 1988, 40 consecutive patients (mean age 54 ± 1.6 years, 85% men, 42.5% with anterior infarction, 10% with prior myocardial infarction) who met the entry criteria from the Intravenous Streptokinase in Acute Myocardial Infarction study[8] and gave informed consent were included in this study. Intravenous thrombolytic treatment consisted of streptokinase (1.5 million units in 45 minutes) in 42.5% of the patients, and of recombinant tissue-type plasminogen activator (70 to 100 mg in 90 to 180 minutes after a bolus of 10 mg) in the remaining 57.5%. Mean delay from pain to thrombolysis was 3.3 ± 0.2 hours (range 0.75 to 7.25). No patient was in cardiogenic shock at the time of inclusion, but 3 patients died in the hospital (1 secondary cardiogenic shock [<12 hours after onset of pain], 1 acute pulmonary edema and 1 electromechanical dissociation within the first days). Emergency angioplasty was performed in 1 patient with anterior infarction in whom thrombolysis did not achieve reperfusion within 5 hours of onset of pain.

Administration of heparin was systematically begun at the end of the infusion of the thrombolytic agent. The heparin dose was adjusted to thromboplastin time. No β blocker, calcium antagonist or antiplatelet therapy was administered before or together with thrombolytic treatment. Lidocaine was administered to 13 patients (32.5%), because of frequent arrhythmias; no other antiarrhythmic drug was used.

Apart from routine medical care, the patients were managed as follows:

Twelve- or 15-lead electrocardiograms were recorded on a simultaneous 3-lead Mingocard 4 electrocardiographic recorder (Siemens-Elema) at the beginning of thrombolytic treatment and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 6, 12, 24 and 48 hours after the beginning of infusion. Continuous electrocardiographic monitoring was performed on an RCM 32 (ELA Medical) monitor.

Blood samples for the determination of plasma levels of creatine kinase (upper value of normal 190 IU/liter) were obtained at the beginning of thrombolytic treatment, and 1, 2, 3, 4, 8, 12, 24 and 48 hours after the beginning of infusion.

Twenty-four-hour 2-channel Holter recording was performed using an ELA 2448 analogic Holter recorder with amplitude modulation and a recording speed of 1 mm/sec (ELA Medical). Holter recording began as soon as possible after admission to the hospital, and the tapes were analyzed on a digital system (Laser Holter, Marquette Electronics). Each morphologic pattern (normal and ventricular complexes) was validated beat after beat. Rhythmic events with the validated ventricular complexes were then defined as isolated ventricular premature complexes (VPCs), couplets or runs of ≥3 beats. Each ventricular run was individually inspected in all patients, studied for its length and rate, and its morphologic pattern was described. The coupling interval of VPCs was measured. The rate of a run was determined from the 2 shortest consecutive RR intervals. All rhythmic events were studied on an hourly basis.

The ventricular arrhythmias studied are further defined as isolated and total VPCs (isolated VPCs and VPCs of the runs), late VPC (coupling interval >1,000 ms), accelerated idioventricular rhythm (run of ≥3 consecutive VPCs at a rate ≤125 beats/min),[9] ventricular tachycardia (VT) (run of ≥3 monomorphic or polymorphic consecutive VPCs at a rate >125 beats/min), sustained (>15 beats) and rapid (>200 beats/min) VT, and ventricular fibrillation.

Coronary angiography was performed as part of the protocol in all patients within 72 hours of onset of pain for the determination of the infarct-related artery patency. Coronary artery patency was assessed by 2 blinded independent observers according to the criteria defined in the Thrombolysis in Myocardial Infarction trial.[10] A group of patients with a patent (grade 2 or 3) artery and a group with a nonpatent (grade 0 or 1) artery were individualized. Left ventricular ejection fraction was calculated from right anterior oblique angiography according to Dodge's method.

Statistical analysis: Quantitative data were expressed as mean ± SEM. Comparisons between groups (patent and nonpatent) were obtained with Student's *t* or Mann-Whitney U test if normality assumptions were violated. Qualitative data were compared using the chi-square test. Presence or absence of the arrhythmia types was used to compute specificity and sensitivity for predicting patency. The independence of quantitative data was tested using bivariate linear correlations. A multiple regression test was used according to a step-down analysis (Statview 512 computer program) for determination of predicting factors of arrhythmias.

TABLE I Incidence and Frequency of Ventricular Arrhythmias Within 24 Hours in Study Patients (n = 40)

Ventricular Arrhythmia	Incidence (%)	Frequency Mean ± SEM (range)
Ventricular premature complexes	40 (100)	2,681 ± 713 (40–16,933)
Late ventricular premature complexes	30 (75)	—
Accelerated idioventricular rhythm	35 (87.5)	116 ± 18 (0–895)
Ventricular tachycardia	32 (80)	28 ± 4 (0–577)
Sustained ventricular tachycardia	11 (27.5)	4.5 ± 2.5 (0–85)
Rapid ventricular tachycardia	10 (25)	1.4 ± 0.6 (0–18)
Ventricular fibrillation	1 (2.5)	—

RESULTS

Holter recordings: Mean time from onset of chest pain to beginning of Holter recording was 3.1 ± 0.2 hours (range 0.66 to 7). Holter monitoring began before thrombolytic therapy in 34 patients (85%) (mean −0.2 hours, maximum −1.5), and after the initiation of thrombolysis in 6 (15%) (mean + 0.3 hours, maximum + 0.7). Mean duration of recording was 23.3 ± 0.5 hours (range 10 to 25.5).

Ventricular arrhythmias: All patients had ventricular arrhythmias. High incidences of VT and accelerated idioventricular rhythm were observed (Table I).

Most runs were short, with 82% of the VTs and 88% of the accelerated idioventricular rhythms having <15 beats (upper range 1,508 and 664 beats, respectively). All runs were self-terminating, and did not need cardioversion or degenerate into ventricular fibrillation.

The hemodynamic status of the patients was not compromised even in the presence of a sustained or rapid VT. Rapid VT was usually short, with 87% of the runs having <15 beats (range 3 to 44). Several and complex configurations of VT were seen. VTs were described according to their morphology (monomorphic or polymorphic), mode of onset, termination and regularity as follows: type 1a: regular monomorphic VT (Figure 1); type 1b: irregular monomorphic VT (Figure 1); type 2: polymorphic VT (Figure 2); type 3: VT induced by monomorphic or polymorphic ventricular "burst" (Figure 3); type 4a: VT ending by a ventricular "burst" (Figure 4); and type 4b: VT ending by an increase in cycle length with or without a change of morphology (Figure 4).

Runs of accelerated idioventricular rhythm could begin on a short or long coupling interval. Fusion beats with sinus rhythm or other accelerated idioventricular rhythms and alternating morphologies were frequently observed (Figure 5).

One patient required cardioversion because of ventricular fibrillation beginning with an R on T phenomenon (Figure 6). No arrhythmic death occurred during the study.

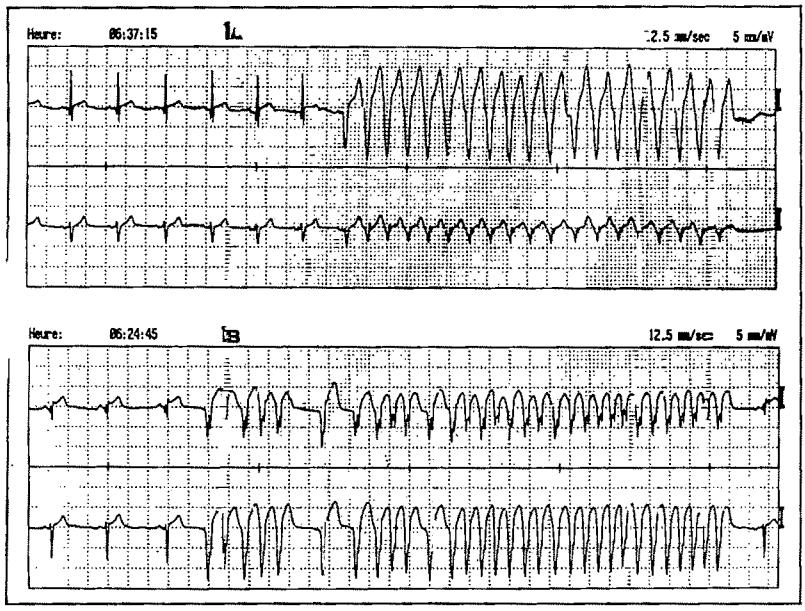


FIGURE 1. Classification of ventricular tachycardias, type 1. Type 1A: monomorphic regular ventricular tachycardia (19 beats, rate = 152 beats/min, duration = 7.92 seconds, shortest cycle length = 395 ms); type 1B: monomorphic irregular ventricular tachycardia (31 beats, rate = 247 beats/min, duration = 10.56 seconds, shortest cycle length = 243 ms, longest cycle length = 896 ms).

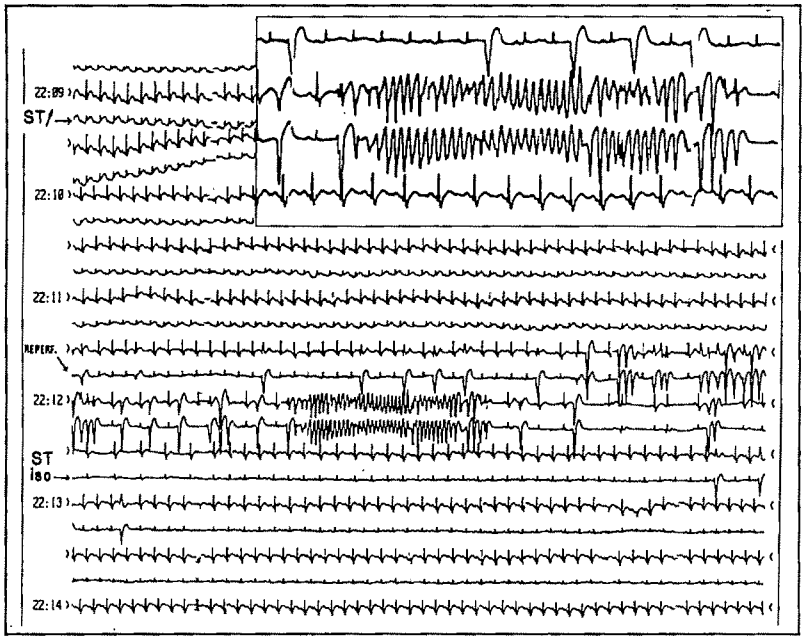


FIGURE 2. Classification of ventricular tachycardias, type 2: polymorphic ventricular tachycardia (44 beats, rate = 300 beats/min, duration = 8.88 seconds; shortest cycle length = 200 ms). Note sudden ST-segment resolution (reperfusion [REPERF.]) <1 minute before onset of arrhythmia.

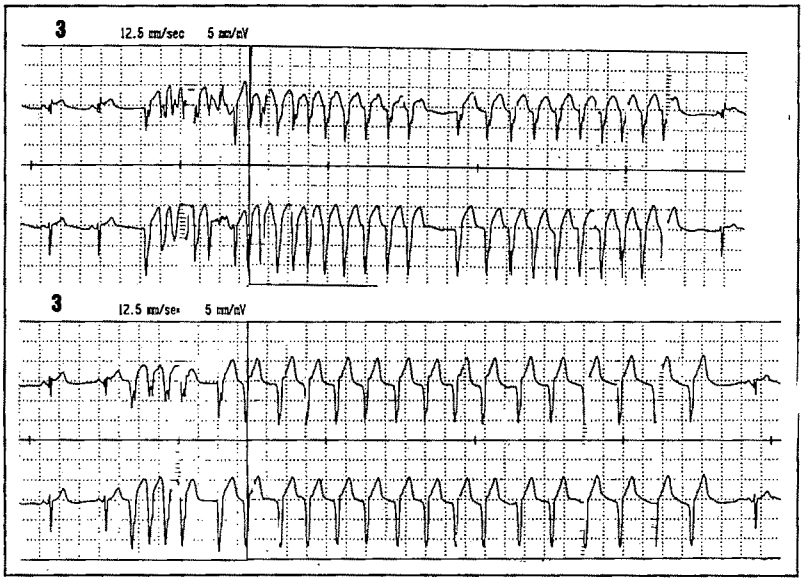


FIGURE 3. Classification of ventricular tachycardias, type 3. *Top,* ventricular tachycardia induced by polymorphic ventricular "burst" (polymorphic burst of 7 ventricular beats, duration of monomorphic ventricular tachycardia = 9.12 seconds, shortest cycle length = 219 ms, longest cycle length = 976 ms); *bottom,* ventricular tachycardia induced by monomorphic ventricular "burst" (monomorphic burst of 4 ventricular beats, duration of monomorphic ventricular tachycardia = 9.78 seconds, shortest cycle length = 333 ms, longest cycle length = 746 ms).

Coronary artery patency: Mean time from onset of chest pain to coronary angiography was 26.7 ± 2.5 hours (range 7.5 to 66.25). Coronary angiography was performed <24 hours after onset of chest pain in 60% of the cases. The infarct-related artery was found to be patent in 29 patients (72.5%). The left anterior descending coronary artery was responsible for the infarction in 17 patients (42.5%), the right coronary artery in 15 (37.5%), and the circumflex lateral coronary artery in 8 (20%). The rate of patency was not significantly different with either thrombolytic agent (streptokinase 59% and recombinant tissue-type plasminogen activator 83%), site of the infarct (anterior 76.5% and nonanterior 70%) or infarct-related artery (left anterior descending coronary artery 76%, right coronary artery 80% and circumflex lateral coronary artery 50%).

Both groups (patent and nonpatent) were not different with regard to baseline characteristics, particularly time to thrombolytic treatment (3.2 ± 0.3 vs 3.4 ± 0.4 hours; p = not significant [NS]) and coronary angiography (27.9 ± 3.2 vs 23.4 ± 4.2 hours; p = NS). Peak creatine kinase occurred within 16 hours of chest pain in 71% of patients in the patent group and in 22% in the nonpatent group (p <0.05).

Ventricular arrhythmias according to coronary artery patency: The prevalence (expressed as percentage

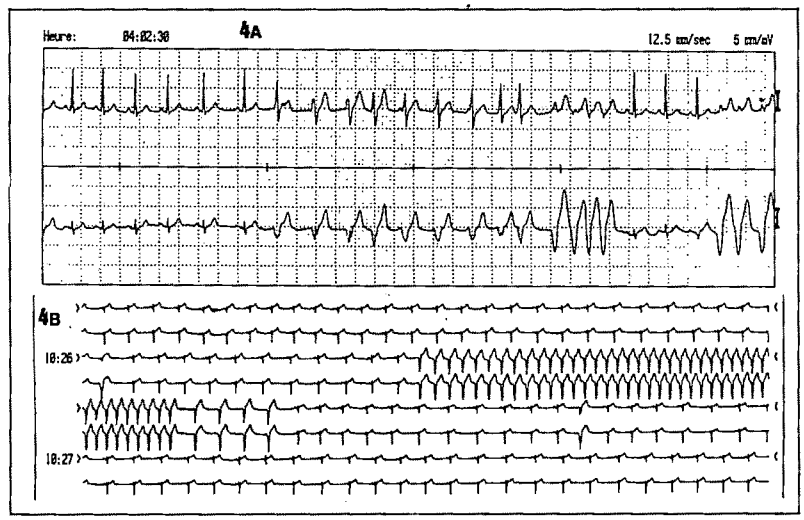


FIGURE 4. Classification of ventricular tachycardias, type 4. Type 4A: ventricular tachycardia ending by ventricular "burst" (monomorphic ventricular tachycardia with long and irregular cycle length leading to monomorphic ventricular burst with shorter cycle length and different morphology; shortest cycle length = 290 ms, longest cycle length = 800 ms). Type 4B: ventricular tachycardia ending by increase in cycle length (monomorphic ventricular tachycardia: 44 beats, rate = 133 beats/min, duration = 23.26 seconds; sudden increase of cycle length [451 to 1,010 ms] terminating tachycardia).

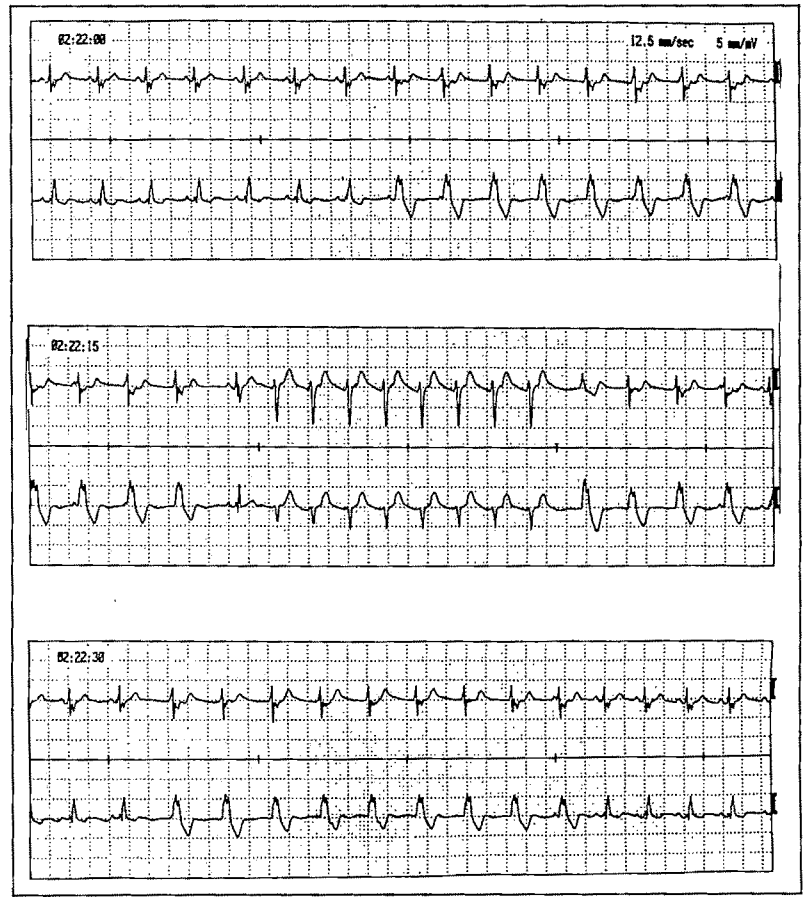


FIGURE 5. Accelerated idioventricular rhythm. Three strips with continuous recording. First strip shows sinus rhythm followed by accelerated idioventricular rhythm. This arrhythmia stops spontaneously in second strip and is followed by conducted sinus beat that is probably fused with first beat of second accelerated idioventricular rhythm. This second arrhythmia also stops spontaneously, after which 4 beats of the first accelerated idioventricular rhythm are seen. Third strip shows recurrence of first accelerated idioventricular rhythm.

TABLE II Incidence and Frequency of Ventricular Arrhythmias in Patients with a Patent and Nonpatent Infarct-Related Artery

Ventricular Arrhythmia	Incidence (%)		Frequency (mean ± SEM)	
	Patent (n = 29)	Nonpatent (n = 11)	Patent (n = 29)	Nonpatent (n = 11)
Total ventricular premature complexes				
24 hours	29 (100)	11 (100)	3,599 ± 930	259 ± 94*
<6 hours	29 (100)	11 (100)	415 ± 134	41 ± 14*
Isolated ventricular premature complexes (24 hours)	29 (100)	11 (100)	1,170 ± 279	210 ± 84*
Late ventricular premature complexes (24 hours)	24 (83)	6 (55)	—	—
Accelerated idioventricular rhythm				
24 hours	26 (90)	9 (82)	158 ± 45	5 ± 3*
<6 hours	22 (76)	2 (18)*	95 ± 30	0.4 ± 0.2*
Ventricular tachycardia				
24 hours	24 (83)	8 (73)	38 ± 21	3 ± 1
<6 hours	13 (45)	3 (27)	21 ± 16	0.6 ± 0.4
Sustained ventricular tachycardia (24 hours)	11 (38)	0 (0)†	6 ± 3	0
Rapid ventricular tachycardia (24 hours)	8 (27)	2 (18)	1.8 ± 0.8	0.4 ± 0.1
Ventricular fibrillation (24 hours)	1 (3)	0 (0)	—	—

*p <0.01; †p <0.05.

of patients with ≥1 episode) and average frequency of the ventricular arrhythmias that we studied in the patent and nonpatent groups are listed in Table II. The time course of the hourly prevalence of VT and accelerated idioventricular rhythm throughout the 24 hours in both groups is shown in Figure 7. No patient in the nonpatent group had >1,000 isolated VPCs (vs 31% in the patent group), >40 couplets (vs 48% in the patent group), >20 runs of VT (vs 17% in the patent group), and >100 runs of accelerated idioventricular rhythm (vs 34% in the patent group) during the 24 hour recording. Persistent runs of accelerated idioventricular rhythm were only seen in patients with a patent artery; all runs in nonpatent patients had <32 beats. The time course of the hourly total frequency of accelerated idioventricular rhythm and VT throughout the 24 hours of recording in both groups is shown in Figure 8.

Factors influencing the onset of ventricular arrhythmias in patients with a patent coronary artery: In patients with a patent infarct-related artery, the incidence and frequency of rhythmic events (VPCs, VT, sustained and rapid VT, accelerated idioventricular rhythm and ventricular fibrillation) were not different when the site of infarct, thrombolytic agent and infarct-related artery were considered.

Lidocaine was administered to 11 patients with a patent coronary artery (38%) and to 2 with a nonpatent coronary artery (18%; p = NS), because of frequent ventricular arrhythmias, according to the clinician's judgment. Clinical parameters (age, sex, site of infarct, time to thrombolytic treatment and coronary angiography, and time to and value of peak creatine kinase) were not different in patients with a patent infarct-related artery regardless of whether they received lidocaine.

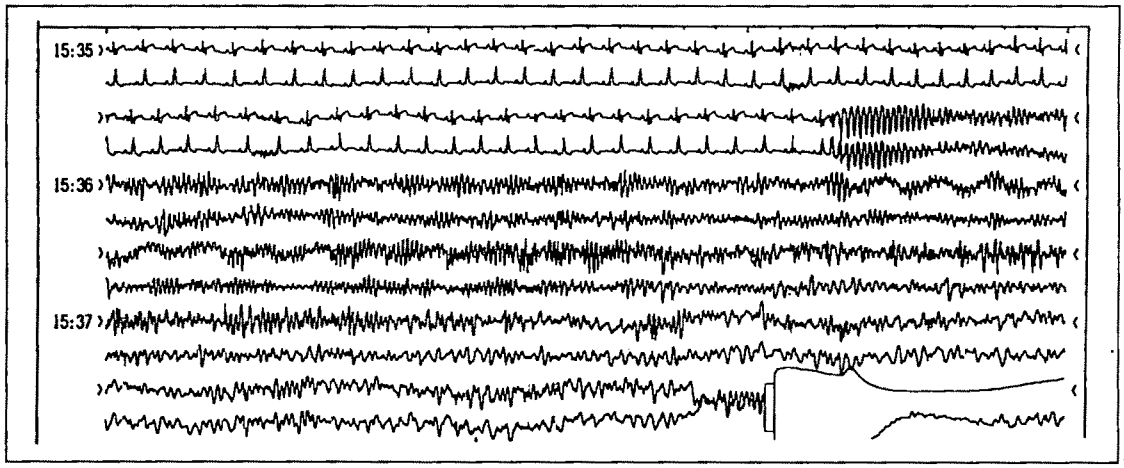


FIGURE 6. Example of ventricular fibrillation probably due to transient reocclusion. Onset of chest pain occurred at 11:25 A.M., and electrocardiographic signs of evolving inferior infarction were documented. Thrombolytic treatment with streptokinase began at 12:10 A.M. Resolution of chest pain and ST-segment normalization were observed at 12:55 A.M., suggesting reperfusion. Recurrence of chest pain with ST-segment elevation suggesting reocclusion was noted at 3:10 P.M. Ventricular fibrillation occurred at 3:35 P.M. without immediate ST-segment change, leading to cardioversion at 3:37 P.M.

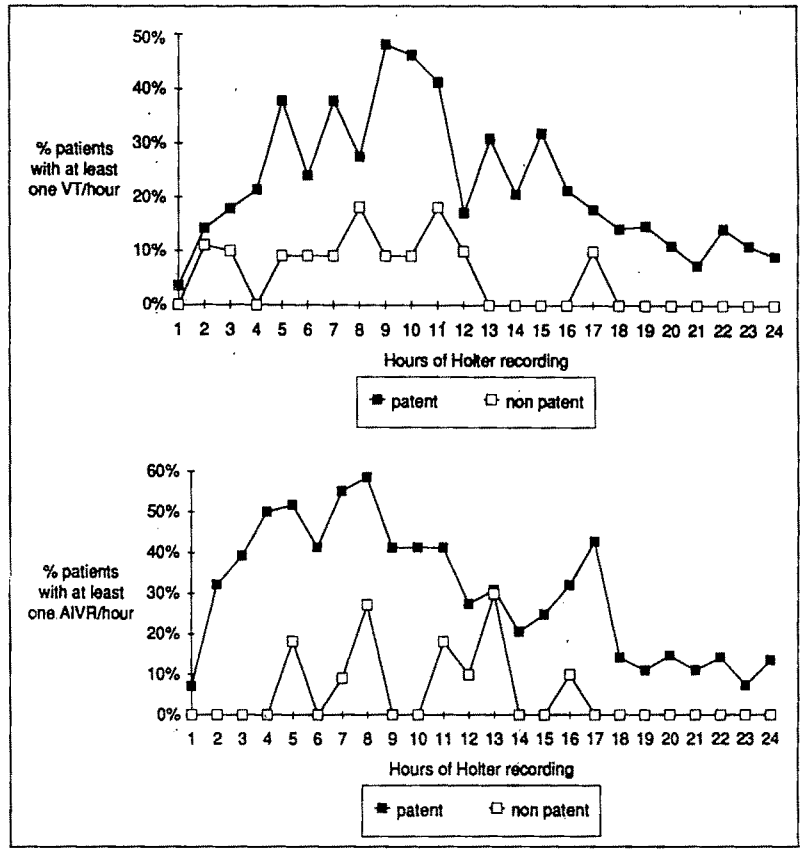


FIGURE 7. Hourly prevalence of ventricular tachycardias (VT) and accelerated idioventricular rhythms (AIVR) according to coronary artery patency.

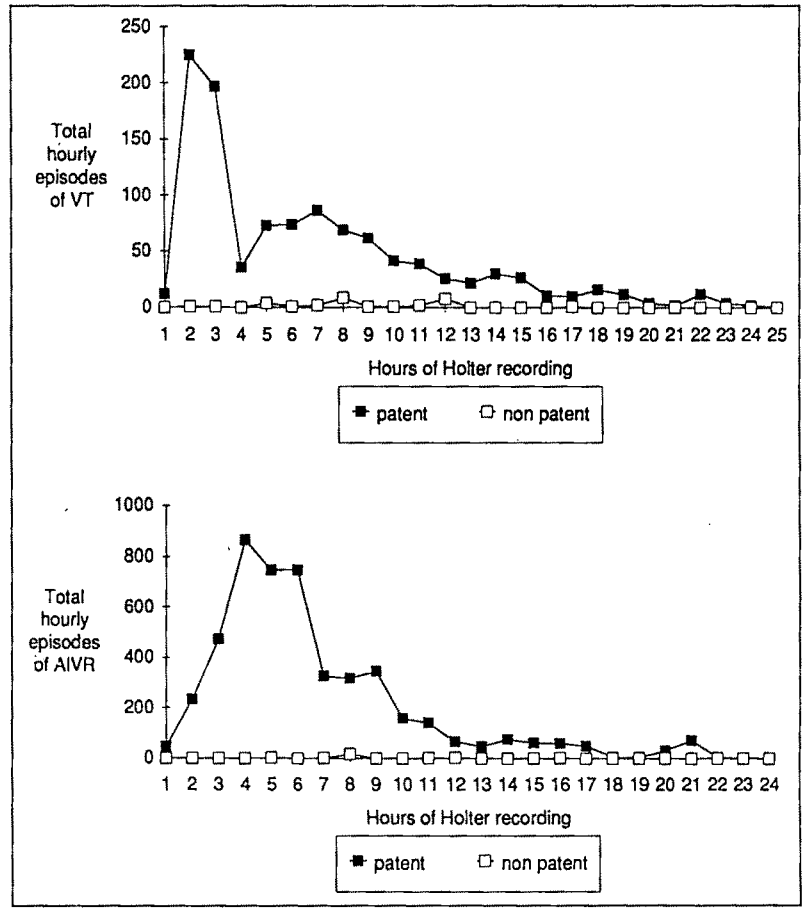


FIGURE 8. Hourly total frequency of ventricular tachycardias (VT) and accelerated idioventricular rhythms (AIVR) according to coronary artery patency.

The incidences of VPCs (100%), VT (91 vs 78%) and accelerated idioventricular rhythm (91 vs 89%) were not different in these 2 groups of patients. The incidences of sustained (64 vs 28%, p = NS) and rapid (55 vs 11%; p <0.05) VT were higher in patients who received lidocaine than in those who had not. The administration of lidocaine in patients with a patent artery was associated with a statistically significant 7-, 23- and 10-fold increase of total VPCs, VT and accelerated idioventricular rhythms, respectively. The difference was still seen in the last 12 hours of recording when all the patients treated with lidocaine were receiving the drug.

No correlation was found between the frequency of VPCs, VT and accelerated idioventricular rhythm, and age and time to thrombolytic treatment. Peak creatine kinase correlated to the frequency of isolated VPCs ($r = 0.47$; $p < 0.02$), total VPCs ($r = 0.43$; $p < 0.05$) and VPCs recorded during the first 6 hours ($r = 0.59$; $p < 0.01$), and to the number of runs ($r = 0.40$; $p < 0.05$) and VTs ($r = 0.40$; $p < 0.05$). Ejection fraction was correlated with the frequency of isolated VPCs ($r = -0.43$; $p < 0.05$), total VPCs ($r = -0.43$; $p < 0.05$) and VPCs recorded during the first 6 hours ($r = -0.5$; $p < 0.05$). No correlation was found between ejection fraction, and the number of VTs and accelerated idioventricular rhythms. Stepwise multiple regression was used with a step-down procedure concerning 2 dependent (VPCs and accelerated idioventricular rhythm within the first 6 hours of recording) and 4 independent (delay of thrombolytic treatment, time to peak creatine kinase, peak creatine kinase and angiographic left ventricular ejection fraction) variables. The final equation for "VPCs within the first 6 hours" is: $Y = -222.85 + 0.256X$ ($p < 0.001$), where X is the variable "peak creatine kinase." Nonsignificant results were obtained with the following variables: times to thrombolytic treatment, to peak creatine kinase and ejection fraction. No independent variable is significant with a p value <0.05 for the variable "accelerated idioventricular rhythm within the first 6 hours."

DISCUSSION

Detection of arrhythmias: Holter recording is the only reliable method for detecting all ventricular arrhythmias. Conventional ward monitoring and electrocardiography detected VPCs, VT or accelerated idioventricular rhythm in only 72% of the patients, which underlines the limits of these methods, even for the detection of rapid and sustained ventricular arrhythmias.

However, Holter recording is not a widely used method during the acute phase of myocardial infarction. In our experience, a computerized analysis cannot be performed as a routine, because of the large number and complexity of the ventricular rhythmic events (polymorphic and irregular runs, and fusion beats) that need simple definitions, and a long and patient validation of the data (range of Holter recording analysis 2 to 24 hours).

Ventricular arrhythmias during the acute phase of myocardial infarction: Ventricular fibrillation is the only arrhythmia that has been properly studied in large trials of thrombolytic therapy in myocardial infarction.[6–7] It is an infrequent arrhythmia (range 3.7 to 6.6%) that occurs as frequently in patients treated with thrombolytic therapy as in control subjects (range 4.6 to 7.5%). Because of the method used for detection and the good tolerance of those arrhythmias, the incidences of VT and accelerated idioventricular rhythm in these studies is very low,[8] which is not in agreement with our conclusions (VT 80%; accelerated idioventricular rhythm 87.5%). Our data are consistent with those from the few studies where the methodology used was similar to ours.[11–13] Thrombolytic therapy appears to increase arrhythmogenicity if one considers that the incidences of VT and accelerated idioventricular rhythm, according to Holter recordings, are 52 and 35%, respectively, as reported by De Soyza et al[14] before the use of this therapy. In agreement with other studies,[11–13] our impression is that these arrhythmias are clinically benign; the figures from the electrocardiograms contrast with a good hemodynamic status and the favorable immediate outcome.

Coronary artery patency: The rate of coronary artery patency in this study is consistent with the literature.[10,15] Coronary angiography only provides an instantaneous view of the artery patency, which does not allow for prediction of the artery status before or after angiography. Thus, our patent group may be heterogeneous, including some patients with a very early reperfusion (whether spontaneous or due to thrombolysis), and others with a later reperfusion (that may even have occurred later than the critical agreed delays for myocardial salvage). The very different myocardial status of patients with a patent infarct-related artery may play a critical role in the onset of reperfusion arrhythmias.

Ventricular arrhythmias during the acute phase of myocardial infarction according to coronary artery patency: The few studies of ventricular arrhythmias during thrombolytic therapy differ in the mode of administration of the thrombolytic agent (intravenous or intracoronary administration, as the latter may induce a more abrupt reperfusion known to be more arrhythmogenic), the criteria for the diagnosis of reperfusion (angiographic or nonangiographic), the time elapsed from onset of pain to the recording of the arrhythmias, the duration of recording and even the definition of the ventricular arrhythmias.[12,13,16–19]

The incidences of accelerated idioventricular rhythm and VT are always higher in patients who are thought to be reperfused (43 to 90 and 85 to 100%, respectively) than in nonreperfused patients (0 to 57 and 25 to 71%, respectively),[13,17,18] but this difference reaches significance in some but not all studies. Though some investigators considered accelerated idioventricular rhythm as suggestive and even specific for reperfusion,[11–13,16–18] we found that they may occur in patients with a nonpatent artery, but their onset seems to be delayed over 5 hours when they may be seen as soon as the first hour in patients with a patent artery. They may be due to transient reperfusion[11] or to the development of collateral vessels. The onset of an early accelerated idioventricular rhythm within the first 6 hours may be considered as a

noninvasive criterion indicative of early coronary patency with a sensitivity of 76% and a specificity of 82%. Sustained VT have seldom been studied, but they may also be considered as a specific (100%) noninvasive criterion indicative of early coronary patency with a low sensitivity of 38%.

In patients with a patent artery, the total numbers of VPCs, VTs and accelerated idioventricular rhythms throughout the 24 hours are multiplied by 14, 13 and 32, respectively, when compared with those of patients with a nonpatent artery. As the only clinical difference between these 2 groups is a patent or nonpatent coronary artery at 24 hours, it is assumed that reperfusion plays a major role in this increase of arrhythmias.

Some investigators have already shown that lidocaine has no effect on ventricular reperfusion arrhythmias,[17,19,20] which is in agreement with our data.

The prognostic significance for late outcome of these early ventricular arrhythmias is not known. Accelerated idioventricular rhythms were reported to be markers of infarction with good prognosis before the era of thrombolysis.[21] We identified a relation between the frequency of rhythmic events and peak creatine kinase. These ventricular arrhythmias may be indicative of poor myocardial outcome.[22]

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Psychosocial Adjustment of Patients Arriving Early at the Emergency Department After Acute Myocardial Infarction

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The psychosocial functioning of patients arriving at the emergency department with an acute myocardial infarction early enough to be candidates for treatment with thrombolytic agents was compared with that of those arriving later. Patients who arrived within 3 hours were significantly more anxious when assessed 1 week after admission and had a consistently worse pattern of psychosocial adjustment 3 months after hospital discharge than did those who arrived later. The implications of these findings for efforts to improve early arrival at the emergency department, as well as for medical and psychosocial outcomes after acute myocardial infarction, were considered.

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Treatment with thrombolytic agents improves survival in patients with acute myocardial infarction (AMI).[1–5] The benefit is substantially greater when patients receive thrombolytic agents early after the onset of AMI.[1–5] Furthermore, early access to medical care is important regardless of whether thrombolytic therapy is administered, because deaths from malignant arrhythmias usually occur early after the onset of AMI.[6] Unfortunately, many patients do not seek immediate treatment. Prolonged delay is the most frequent contraindication to use of thrombolytic agents.[1–5] Therefore, many physicians advocate programs designed to minimize such delays.

Little is known about the psychosocial functioning of patients who arrive early compared with that of those who arrive later. Because early arrival is likely to improve medical prognosis, such patients may also have a better psychosocial outcome. However, these patients may arrive early because they are anxious, depressed or somatically preoccupied. These factors are known to predict adverse psychosocial outcomes, independent of medical status.[7–5] Accordingly, we compared the psychosocial functioning during hospitalization and 3 months after discharge of patients with initial Q-wave AMI who arrived at the emergency department early (i.e., within the window of opportunity for thrombolytic therapy) with that of those who arrived later.

METHODS

Subjects: Subjects were recruited from a sequential series of patients with documented Q-wave AMI who were admitted to the cardiac care unit. Patients included in the study had to be: (1) aged <70 years, (2) able to recall the time of onset of symptoms of AMI, (3) able to undergo an interview and psychometric assessment, (4) willing to provide informed consent, and (5) permitted by their cardiologist to participate. Patients were excluded from the study if they: (1) had history of AMI, coronary disease or any cardiac procedure, including catheterization, (2) had congestive heart failure or valvular heart disease (except mitral valve prolapse), (3) had any other chronic medical illness, (4) had significant cognitive impairment as determined by a mini-mental status examination, or (5) were located farther than a 30-minute drive from the hospital at the time of onset of symptoms.

Forty-two of 124 patients screened for recruitment met these criteria and were enrolled within 5 days of AMI. During this study patients were eligible for thrombolytic treatment only if they arrived within 3 hours after the onset of symptoms. Accordingly, patients who arrived within 3 hours were classified as early arrivers, and patients who arrived later were classified as late arrivers.

Procedure: ASSESSMENT DURING HOSPITALIZATION: Patients were administered the Hopkins Symptom Checklist 90, Revised.[10] The Symptom Checklist is a widely used self-report measure of somatization, depression, anxiety, obsessive-compulsive symptoms, interpersonal sensitivity, phobic anxiety, hostility, paranoid ideation and psychoticism. Patients were also administered the Jenkins Activity Survey,[11] a self-report measure of the type A behavior pattern. The times of symptom onset and arrival to the emergency department were documented by the emergency department staff and noted in each patient's chart.

FOLLOW-UP: Three months after hospital discharge, patients were administered the Psychosocial Adjust-

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TABLE I Demographic and Medical Characteristics at Index Hospitalization

	Early Arrivers	Late Arrivers
Age	54 ± 10	51 ± 8
Married	36 (86%)	33 (79%)
Men/women	33/9	30/12
Severity of CAD*	1.83 ± 1.03	1.80 ± .92
LVEF	51 ± 14	49 ± 16
Percentage of AMIs occurring during daytime	61%	57%

*Number of vessels occluded ≥ 50%.
AMIs = acute myocardial infarctions; CAD = coronary artery disease; LVEF = left ventricular ejection fraction.

ment to Illness Scale,[12] a self-report measure of psychosocial adjustment to medical illness in terms of general health, work capacity, domestic atmosphere, sexual performance, family and social support, and psychological distress.

RESULTS

Twenty-five patients arrived at the emergency department within 3 hours after the onset of symptoms (mean 1.4 ± 0.7), and 17 arrived after 3 hours (mean 5.5 ± 8.2). No late arriver and 17 early arrivers (68%) received treatment with thrombolytic agents.

Twenty-four early and 15 late arrivers subsequently underwent cardiac catheterization. There were no differences between the 2 groups in left ventricular function or severity of coronary artery disease (Table I). There were also no differences in any of the other medical and demographic variables that were assessed.

Psychological test results during hospitalization are listed in Table II. Early arrivers scored significantly higher on the anxiety and phobic anxiety scales of the Symptom Checklist. None of the other scores were significantly different between the groups. There was no difference between the groups on the Jenkins Activity Survey. All but 1 of the early (96%) and 1 of the late (94%) arrivers completed the follow-up assessment (Table III). The number of subjects varied slightly (38 to 40) across analyses, because certain items or subtests (e.g., employment-related questions) were not applicable in some cases. Early arrivers scored significantly higher on all 7 subtests of the Psychosocial Adjustment to Illness Scale, suggesting a worse pattern of psychosocial adjustment to illness during the 3 months after the initial AMI.

DISCUSSION

This study found that early arrivers were more anxious than later arrivers and had a worse psychosocial adjustment at 3 months. Moreover, early arrivers scored nonsignificantly higher on all but 1 scale of the Symptom Checklist, suggesting the possibility of greater general emotional distress than that of late arrivers. No patient in either group had history of cardiac disease. All patients reported chest pain during AMI. Thus, there were no identifiable differences in medical history or symptoms that may have influenced the decision to go to the hospital. Furthermore, no differences in demographic characteristics on admission or in extent of cardiovascular disease were subsequently found. Consequently, the psychosocial differences that were found cannot be easily explained by differences in demographics, ventricular function or disease severity.

TABLE II Comparison of Jenkins Activity Survey and Symptom Checklist for Patients Arriving to the Emergency Department Early Versus Late

Scales	Early Arrivers*	Late Arrivers*	t	p Value
Jenkins Activity Survey				
Type A score	248 ± 87	243 ± 73	0.88	NS
Symptom checklist				
Somatization	1.1 ± 0.8	0.7 ± 0.7	1.57	NS
Obsessive-compulsive	0.7 ± 0.7	0.5 ± 0.7	0.87	NS
Interpersonal sensitivity	0.4 ± 0.5	0.5 ± 0.7	−0.11	NS
Depression	0.9 ± 0.9	0.6 ± 0.8	1.11	NS
Anxiety	0.7 ± 0.8	0.3 ± 0.5	1.97	<0.05
Hostility	0.5 ± 0.8	0.3 ± 0.4	1.08	NS
Phobic anxiety	0.3 ± 0.6	0.1 ± 0.2	1.99	<0.05
Paranoid ideation	0.5 ± 0.5	0.3 ± 0.4	0.87	NS
Psychoticism	0.4 ± 0.5	0.2 ± 0.3	1.58	NS
Positive symptom total	30.2 ± 21.1	20.8 ± 18.8	1.48	NS
Global severity index	0.7 ± 0.6	0.4 ± 0.6	1.48	NS

*Mean ± standard deviation.
NS = not significant.

TABLE III Comparison of the Psychosocial Adjustment to Illness for Early Versus Late Arrivers at Three-Month Follow-Up

Subscale	Early Arrivers*	Late Arrivers*	t	p Value
Health care orientation	13.5 ± 4.2	10.9 ± 5.4	2.12	0.04
Vocational environment	10.0 ± 2	8.7 ± 2.7	1.90	0.06
Domestic environment	14.4 ± 3.1	11.6 ± 4.2	2.92	0.006
Sexual relations	10.0 ± 2.6	8.4 ± 4.3	1.98	0.05
Extended family	6.8 ± 2.2	5.4 ± 3.1	2.36	0.02
Social environment	9.3 ± 2.1	7.9 ± 3	2.36	0.02
Psychological distress	11.7 ± 3.2	9.3 ± 4.2	2.69	0.01

*Mean ± standard deviation.

This outcome could be an unexpected effect of thrombolytic treatment rather than of early arrival. To test this hypothesis, we compared the 7 scales of the Psychosocial Adjustment to Illness Scale of the 8 patients who did not receive thrombolytic therapy, despite arriving early enough to the emergency department to be eligible, with the scores of the 17 who did receive it. There were no differences on any of the 7 scales. In fact, the means were nearly identical ($p > 0.60$). Thus, poorer psychosocial adjustment appears to be associated with relatively early arrival at the emergency department and not with thrombolytic therapy.

It is possible that the patients who arrived early may have done so in part because they were more anxious than were the later arrivers after the onset of AMI. However, it is possible that the early arrivers became more anxious after their hospital admission for reasons that are currently unclear. In any case, there may be reason to be concerned. Previous studies have documented increased mortality and both medical and psychological morbidity in anxious, depressed or stressed patients with a recent AMI.[13–16] If anxiety or other forms of emotional distress are detected in early arrivers, these patients may need psychological treatment af-

ter they are medically stabilized. If their anxiety were treated after admission, both the long-term medical and psychosocial prognosis of these patients may be improved.

There is already evidence that such an intervention may have a beneficial effect. Frasure-Smith and Prince[17] randomly assigned patients after AMI to either standard care or standard care plus, a stress reduction intervention. After 1 year, these patients had lower stress scores and fewer cardiac deaths than did control subjects.

Earlier studies documented other psychological differences between late and early arrivers to the emergency department after the onset of AMI. Theorell et al[18] found that the inability to relax during leisure time (an aspect of the type A behavior pattern) was associated with a shorter delay in arrival. However, Matthews et al[19] found that patients who delayed in deciding that they were ill after onset of symptoms tended to exhibit type A behavior. Patients who delayed seeking treatment after deciding they were ill tended to exhibit type B behavior. We did not find differences between our early and late arrivers on our type A measure. Matthews used the Structured Interview to assess the type A behavior pattern, whereas we used the Jenkins Activity Survey self-report inventory. The Interview may be more sensitive than the Jenkins scale to the relevant type A features.

Although denial was not assessed in this study, it is possible that patients who arrived late were less anxious than early arrivers, because they were denying the seriousness or even the reality of their AMI. However, Hackett and Cassem[20] did not find a relation between denial and time of arrival to the emergency department in patients with AMI. They found that other factors (such as another person insisting that the patient go to the emergency department) played a more important role. Many patients engage in some form of denial after AMI, and this denial is usually associated with reduced anxiety while in the cardiac care unit.[21] Levine et al[22] found that patients who strongly denied their illness tended to spend fewer days in the cardiac care unit and had fewer signs of cardiac dysfunction during hospitalization. However, in the year after hospital discharge, strong deniers adapted more poorly. Our late arrivers, however, continued to do well 3 months after discharge. The role of denial in late arrival needs further investigation.

In conclusion, this study found that patients who arrived at the hospital early after onset of symptoms were more anxious during hospitalization and had a worse psychosocial adjustment in the 3 months after AMI. Psychotherapeutic intervention may be useful in these patients, because studies have shown that high levels of anxiety after AMI are associated with a poor medical prognosis and worse psychosocial adjustment. In addition, further research is needed to develop strategies that encourage early hospital admission without unnecessarily increasing anxiety. Unfortunately, the conclusion of Hackett and Cassem[21] nearly 25 years ago still applies today: ". . . we know almost nothing about the social, psychological, or genetic factors that facilitate or inhibit the process of delay. . . ." Further research with larger samples of patients is clearly needed to delineate the psychological and social determinants of the decision to go to the emergency department when symptoms of AMI occur, and to understand the factors affecting the psychosocial adjustment of early arrivers.

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Effect of Timolol on Cardiopulmonary Exercise Performance in Men After Myocardial Infarction

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The effect of the nonselective β blocker timolol on maximal cardiopulmonary exercise performance was evaluated in 28 men with previous myocardial infarction without effort angina (mean age 63 ± 8 years). Patients were randomized to placebo or timolol (10 mg twice daily) for 4 weeks and then crossed over to the alternative therapy in a double-blind manner. At the completion of each treatment period, patients underwent symptom-limited maximal cardiopulmonary exercise on a cycle ergometer. Exercise time, heart rate, oxygen consumption ($\dot{V}O_2$), oxygen (O_2) pulse and respiratory exchange ratio were measured at peak exercise and at a submaximal exercise level defined at a respiratory exchange ratio of 1.00. Timolol treatment reduced peak heart rate from 153 ± 11 to 102 ± 14 beats/min (−33%, p <0.001). Exercise time decreased from 680 ± 91 to 633 ± 78 seconds (−7%, p <0.001). Peak $\dot{V}O_2$ decreased from 25.3 ± 4.7 to 21.4 ± 3.5 ml/min/kg (−15%, p <0.001). O_2 pulse increased from 12.9 ± 1.9 to 16.7 ± 2.3 ml/beat (+29%, p <0.001). Peak respiratory exchange ratio did not change significantly, indicating comparable effort. At submaximal exercise, defined at a respiratory exchange ratio of 1.00, there was no difference in exercise time between placebo and timolol. Heart rate decreased with timolol compared with placebo, from 126 ± 16 beats/min by 31% (p <0.001), $\dot{V}O_2$ decreased from 18.5 ± 4.3 ml/min/kg by 10% (p <0.001), O_2 pulse increased from 11.5 ± 2.0 ml/beat by 30% (p <0.001).

The results indicate that timolol significantly reduced peak $\dot{V}O_2$, heart rate and exercise time at peak exercise. The increased O_2 pulse at maximal level of exercise only partially compensated for the reduction in heart rate. At submaximal exercise, $\dot{V}O_2$ and heart rate were reduced during timolol treatment, and the increase in O_2 pulse more completely compensated for the reduced heart rate. The results indicate that the use of β blockade for secondary prophylaxis substantially compromises functional capacity at peak and submaximal exercise.

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Nonselective β-blocking agents have been shown to reduce mortality in survivors of myocardial infarction.[1,2] These agents are therefore widely used for secondary prophylaxis after myocardial infarction.[3] Therapy has been shown to improve exercise performance in patients with symptomatic ischemia.[4–6] The effects of β-blocking agents on exercise performance in healthy subjects have been evaluated, and both reduced[7,8] and unchanged[9,10] peak oxygen consumption ($\dot{V}O_2$) have been reported. In untrained healthy subjects the β-blockade mediated reduction in peak heart rate has a minimal effect on peak $\dot{V}O_2$.[9,11] Increase in stroke volume and arterial-mixed venous oxygen (O_2) difference compensate for the negative chronotropic effect.[12–14] In trained subjects, β blockade is associated with reduction in peak $\dot{V}O_2$.[11,15] In patients with atrial fibrillation there is a reduction in $\dot{V}O_2$ both at maximal and submaximal exercise.[16] An attenuation of the improved performance after exercise training programs has been reported in patients receiving β-blocking agents after myocardial infarction.[15,17]

The present study was designed to quantify the effects of β blockade on cardiopulmonary exercise performance in patients with previous myocardial infarction. Patient who did not have postinfarction angina or electrocardiographic evidence of ischemia during maximal symptom-limited exercise were selected. The patient group given β-blocker therapy for secondary prophylaxis is substantial, and evaluation of exercise capacity in this patient group is important to in order to assess the efficacy of training programs and medical intervention.

METHODS

Patient group: Thirty-two men were entered into the study and 28 completed the protocol. All patients had a history of documented myocardial infarction at least 1 year before inclusion. All patients had been given chronic β-blocker therapy after myocardial infarction for secondary prophylaxis. None of the patients reported effort angina or showed electrocardiographic evidence of ischemia. The patients were familiar with both the gas exchange equipment and the personnel at the exercise laboratory from participation in a previous trial.[18] None of the patients had clinical signs of congestive heart failure, and all were in New York Heart Association functional class I. Clinical details are provided in Table I. The study protocol was approved by the Regional Hospital Ethical Committee and the Norwegian State Drug Regulatory Agency.

Study design: After a 4-week open washout period without timolol, the patients underwent a screening test. Symptoms or signs of ischemia precluded participation

TABLE I Clinical Characteristics (n = 32)

Age (years)	63 (±8)
Systolic BP (mm Hg)	137 (±16)
Diastolic BP (mm Hg)	83 (±7)
HR at rest (beats/min)	84 (±11)
Weight (kg)	79.6 (±9.3)
Q-wave MI	26
Anterior MI	9
Inferior MI	22
Peak CKB (U/liter)	97 (±66)
Peak ASAT (U/liter)	199 (±121)
Peak LD1 (U/liter)	851 (±527)
X-ray heart size (ml/m^2)	512 (±83)
Echo. LV diameter (mm)	59 (±5)
Exercise time (sec)	631 (±115)
Peak HR (beats/min)	156 (±12)
Peak $\dot{V}O_2$ (ml/kg/min)	25.3 (±4.6)
Peak VE (liters/min)	77 (±17)
Peak O_2 pulse (ml/beat)	13 (±2)
Peak RER ($\dot{V}CO_2/\dot{V}O_2$)	1.19 (±0.09)

Values are expressed as mean ± standard deviation.
ASAT = aspartate aminotransferase; BP = blood pressure; CKB = creatine phosphokinase; Echo. = echocardiographic; HR = heart rate; LD1 = lactate dehydrogenase; LV = left ventricular; MI = myocardial infarction; O_2 pulse = $\dot{V}O_2$/HR;RER = respiratory exchange ratio; $\dot{V}CO_2$=carbon dioxide elimination; VE = ventilation; $\dot{V}O_2$= oxygen consumption.

in the study. After this first baseline test the patients were randomized to oral timolol 10 mg twice daily or matched placebo in a double-blind fashion. After 4 weeks on therapy, patients were tested, followed by 1 week of gradual withdrawal of study medication. Patients then were tested after 4 weeks without treatment, (second baseline test). The patients were then crossed over to alternative treatment in a blinded fashion. After 4 weeks in this second treatment period the patients underwent a fourth test. The total study duration was 18 weeks for each patient. Because of the gradual reduction in study medication after treatment periods, the 2 baseline periods were single-blinded. This period with placebo medication provided sufficient washout time for timolol, and minimized the risk of carryover effects.[19]

Exercise protocol: Patients underwent maximal symptom-limited exercise on an electrically braked bicycle ergometer (Mijnhardt model KEM III) programmed for a continuous ramp protocol corresponding to increments of 20 W/min. Patients rested for 2 minutes on the bicycle before exercise. Gas exchange indexes and ventilation data were collected during exercise on a breath-by-breath basis using a computerized system (Medical Graphics Corporation system 2001) according to methods previously described.[20,21] The method uses a distributive processing technique involving a waveform analyzer and a host computer. Expired air flow, carbon dioxide (CO_2) and O_2 partial pressure are measured using rapid responding discrete analyzers; a pneumotachometer and variable-reluctant pressure transducer for flow, a dual-beam infrared absorbtion chamber for CO_2, and a permanent zirconia-based electrochemical cell for O_2.[22] A 12-lead electrocardiograph (Kone 620) was interfaced and heart rate recorded continuously. Blood pressure was measured every 3 minutes against mercury.

Data analysis: Respiratory data were collected at peak exercise and submaximal exercise. Peak $\dot{V}O_2$ was determined as the average of values obtained during the final 20 seconds of exercise. The reproducibility of gas exchange indexes at peak exercise is well established.[23,24] The submaximal level of exercise was defined at a time point when the respiratory exchange ratio reached 1.00, and was stable for ≥20 seconds. It has been shown that a respiratory exchange ratio of 1.00 correlates well with the gas exchange anaerobic threshold and approximates a serum lactate concentration of 2 mmol/liter.[20] This submaximal index has been shown to be predictive of peak exercise performance.[25] Exercise time, heart rate, $\dot{V}O_2$, CO_2 production ($\dot{V}CO_2$), O_2 pulse, ventilation and respiratory exchange ratio ($\dot{V}CO_2/\dot{V}O_2$) were calculated at peak exercise and at a respiratory exchange ratio of 1.00, and at 60% of total exercise time.

Treatment differences were analyzed using Student's *t* test for paired samples. The reproducibility of the 2 baseline tests is expressed by the standard deviation of the mean difference between baseline 1 and 2. By design, each active treatment period was preceded by a baseline test in order to evaluate possible sequence or carryover effects.

RESULTS

Twenty-eight patients completed the study according to protocol. All patients received 10 mg of timolol or placebo twice daily. Four patients were excluded after initial randomization. One patient developed angina during withdrawal of β-blocker therapy and one patient experienced symptomatic hypotension with treatment. Two patients did not complete the trial due to unrelated concurrent illness. No clinically relevant dysrhythmia occurred during testing.

The mean ± standard deviation difference between the 2 baseline tests was 0.4 (±2.6) ml/kg/min for peak $\dot{V}O_2$, and 3 (±47) seconds for peak exercise time (p = not significant). At a respiratory exchange ratio of 1.00, the difference between the baseline tests was 1.1 (±2.8) ml/kg/min for $\dot{V}O_2$, and 19 (±62) seconds for exercise time (p = not significant). There were no significant differences between the first and second baseline tests for any of the exercise parameters. Table II provides details.

The difference in peak $\dot{V}O_2$ between placebo and timolol was −3.15 ± 1.57 ml/kg/min when timolol was given in the first treatment period. The difference in peak $\dot{V}O_2$ between placebo and timolol was −4.8 ± 3.9 ml/kg/min when timolol was given in the second treatment period. These differences were not significant using the Kolmogorov-Smirnov test, and this result argues against a substantial carryover effect.

Compared with placebo, timolol treatment resulted in reduced exercise performance at maximal symptom-limited exercise. Peak $\dot{V}O_2$ decreased from 25.3 ± 4.7 ml/min/kg by 15% (p <0.001), exercise time decreased from 680 ± 91 seconds by 7% (p <0.001), heart rate decreased from 153 ± 11 beats/min by 33% (p

TABLE II Results at Peak Exercise

	Placebo Baseline	Timolol Baseline	Difference	p Value
ET (sec)	667 (±87)	669 (±79)	3 (±47)	NS
HR (beats/min)	153 (±13)	153 (±11)	0 (±10)	NS
$\dot{V}O_2$ (ml/kg/min)	24.4 (±4.6)	24.8 (±4.1)	0.4 (±2.6)	NS
$\dot{V}CO_2$ (ml/min)	2,296 (±418)	2,325 (±365)	29 (±219)	NS
VE (liters/min)	76.8 (±15.7)	78.3 (±15.8)	1.5 (±7.1)	NS
O_2 pulse (ml/beat)	12.5 (±1.7)	12.8 (±1.9)	0.3 (±1.2)	NS
RER ($\dot{V}CO_2/\dot{V}O_2$)	1.19 (±0.08)	1.19 (±.08)	0 (±0.05)	NS

Values are expressed as mean ± standard deviation.
ET = exercise time; NS = not significant; other abbreviations as in Table I.

TABLE III Results at Peak Exercise

	Placebo	Timolol	Difference	p Value
ET (sec)	680 (±91)	633 (±78)	−47 (±45)	<0.001
HR (beats/min)	153 (±11)	102 (±14)	−51 (±13)	<0.001
$\dot{V}O_2$ (ml/kg/min)	25.3 (±4.7)	21.4 (±3.5)	−3.9 (±3.0)	<0.001
$\dot{V}CO_2$ (ml/min)	2,352 (±400)	2,051 (±369)	−301 (±239)	<0.001
VE (liters/min)	78.7 (±14.4)	69.1 (±13.5)	−9.6 (±9.0)	<0.001
O_2 pulse (ml/beat)	12.9 (±1.9)	16.7 (±2.3)	3.8 (±1.7)	<0.001
RER ($\dot{V}CO_2/\dot{V}O_2$)	1.19 (±0.09)	1.21 (±0.08)	0.02 (±0.07)	NS

Values are expressed as mean ± standard deviation.
Abbreviations as in Tables I and II.

TABLE IV Results at Submaximal Exercise (RER = 1)

	Placebo	Timolol	Difference	p Value
ET (sec)	474 (±99)	462 (±76)	−12 (±59)	NS
HR (beats/min)	126 (±16)	87 (±12)	−39 (±13)	<0.001
$\dot{V}O_2$ (ml/kg/min)	18.5 (±4.3)	16.6 (±3.3)	−1.9 (±2.8)	<0.001
$\dot{V}CO_2$ (ml/min)	1,473 (±313)	1,321 (±249)	−152 (±206)	<0.001
VE (liters/min)	45.3 (±7.6)	41.9 (±6.6)	−3.4 (±5.2)	<0.01
O_2 pulse (ml/beat)	11.5 (±2.0)	15.0 (±2.3)	3.5 (±1.6)	<0.001

Values are expressed as mean ± standard deviation.
Abbreviations as in Tables I and II.

TABLE V Results at Submaximal Exercise (60% of peak exercise time)

	Placebo	Timolol	Difference	p Value
HR (beats/min)	122 (±11)	86 (±10)	−36 (±9)	<0.001
$\dot{V}O_2$ (ml/kg/min)	17.2 (±2.8)	15.9 (±2.8)	−1.3 (±1.7)	<0.001
VE (L/min)	41.8 (±7.4)	38.4 (±6.1)	−3.4 (±4.7)	<0.001
O_2 pulse (ml/beat)	11.1 (±1.8)	14.8 (±2.4)	3.7 (±1.4)	<0.001
RER ($\dot{V}CO_2/\dot{V}O_2$)	0.98 (±0.07)	0.98 (±0.07)	0.00 (±0.07)	NS

Values are expressed as mean ± standard deviation.
Abbreviations as in Tables I and I.

<0.001), minute ventilation decreased from 78.7 ± 14.4 liters/min by 12% (p <0.001) and O_2 pulse increased from 12.9 ± 1.9 ml/beat by 29% (p <0.001). There were no significant differences in respiratory exchange ratio between the 2 treatment periods (1.19 ± 0.09 with placebo vs 1.21 ± 0.08 with timolol). Table III provides mean results for placebo and timolol treatment at peak exercise.

At a respiratory exchange ratio of 1.00 we observed no significant change in exercise time with timolol treatment versus placebo (474 ± 99 vs 462 ± 76 seconds). Heart rate decreased from 126 ± 16 beats/min by 31% (p <0.001), peak $\dot{V}O_2$ decreased from 18.5 ± 4.3 ml/kg/min by 10% (p <0.001), and minute ventilation decreased from 45.3 ± 7.6 liters/min by 7.5% (p <0.01). O_2 pulse increased from 11.5 ± 2.0 ml/beat by 30% (p <0.001). Table IV summarizes mean results of the tests after treatment periods at submaximal exercise defined at a respiratory exchange ratio of 1.00.

At a submaximal level of exercise defined at 60% of peak exercise time in the first baseline test there was no significant difference in the respiratory exchange ratio (0.98 ± 0.07 with placebo vs 0.98 ± 0.07 with timolol). With timolol treatment, peak $\dot{V}O_2$ decreased from 17.2 ± 2.8 ml/min/kg by 7.5% (p <0.001), heart rate decreased from 122 ± 11 beats/min by 30% (p

<0.001) and minute ventilation decreased from 41.8 ± 7.4 liters/min by 8% (p <0.001). O_2 pulse increased from 11.1 ± 1.8 ml/beat by 33% (p <0.001). Table V provides details.

DISCUSSION

The main finding in this study is that nonselective β blockade with timolol substantially reduces exercise performance in men with previous myocardial infarction without exercise-induced ischemia. The effect is documented by reduced exercise duration (−7%) and peak O_2 consumption (−15%) during cardiopulmonary exercise testing. There were no differences in mean peak respiratory exchange ratio with placebo versus timolol, which confirms maximal and comparable effort. A similar response at submaximal exercise was observed (Figure 1).

Patients without postinfarction angina or electrocardiographic evidence of ischemia during maximal symptom-limited exercise were selected. Our experience suggests that maximal exercise performance is more readily achieved in men and we therefore limited inclusion to male patients. In a population of patients with myocardial infarction, it is not unlikely that some patients did indeed develop ischemia during exercise, and 1 patient had to discontinue the study owing to effort angina after withdrawal of β-blocker treatment. In patients with exercise-induced ischemia β blockade may improve exercise duration.[4] The attenuated chronotropic response during β blockade will increase diastolic coronary perfusion time. Along with a reduction in myocardial O_2 consumption mediated by decreased inotropy during β blockade, the lower heart rate may contribute to a prolongation of exercise before the ischemic event.[5] Silent ischemia during exercise should improve with β-blocker treatment,[6] and would serve to attenuate the observed reduction in exercise capacity.

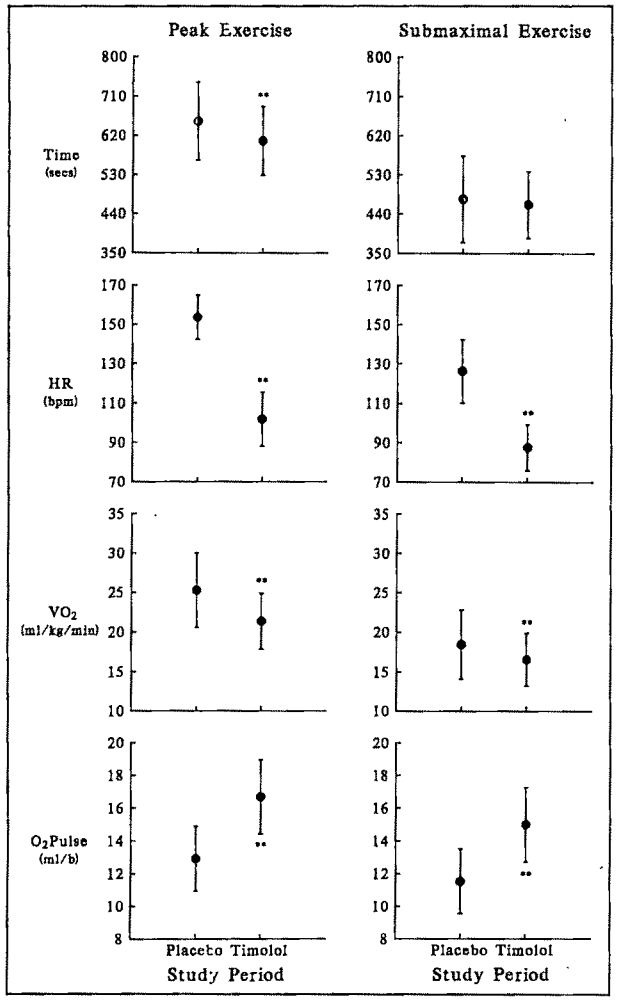


FIGURE 1. Comparison of gas exchange parameters with timolol versus placebo at peak and at submaximal (respiratory exchange ratio = 1.00) exercise (n = 28). HR = heart rate; O_2Pulse = oxygen consumption/heart rate; VO_2 = oxygen consumption; **p <0.001.

The study was not designed to elucidate the mechanisms by which β blockade limits exercise performance. However, the marked negative chronotropic response suggests that this is the primary mechanism. In healthy subjects, cardiac output and exercise performance is maintained with nonselective β-blocker therapy.[26] Reduction in heart rate induced by β blockade is compensated for by an increase in stroke volume, mediated by an increase in left ventricular end-diastolic volume according to the Frank-Starling mechanism.[9]

In patients with documented myocardial infarction, it is reasonable to postulate that the ability to increase stroke volume during exercise is limited because of the loss of myocardial tissue. Therefore, cardiac output becomes more dependent on an adequate chronotropic response.[27] It has been shown that in patients with symptomatic left ventricular failure, no increase in ejection fraction occurs during exercise and cardiac output becomes a function of heart rate.[28,29]

The ability of exercising muscular tissue to perform work is dependent on its supply of O_2. The O_2 consumption in working skeletal muscular tissue is a function of local blood flow and the capacity in the muscle to extract O_2. Adrenergic stimulation of β_2 receptors during exercise results in arteriolar dilatation to exercising muscle with increased blood flow.[30] Nonselective β blockade may attenuate this vasodilatation, and substantially contribute to the observed reduction in $\dot{V}O_2$ observed in our study.[11]

At submaximal exercise, defined as a respiratory exchange ratio of 1.00, we observed a reduction in $\dot{V}O_2$ of 10% and a reduction in heart rate of 31%, comparable to the results observed at peak exercise. We did not observe a reduction in exercise time in the timolol treatment period compared with the placebo period. This implies that the work performed during submaximal exercise was not affected by timolol treatment. The O_2 pulse increased by 30% at submaximal exercise. This increase in O_2 pulse appears to compensate more completely for reduction in heart rate at submaximal exercise as the work load reached was not affected with timolol treatment.

It has recently been demonstrated that nonselective β blockade decreases forced vital capacity and forced

expiratory volume in 1 second,[8] suggesting inhibition of β_2 adrenergic-mediated bronchodilatation. We observed reduced minute ventilation both at submaximal (-3.4 ± 5.2 liter/min, $p < 0.01$) and maximal (-9.6 ± 9.0 liters/min, $p < 0.001$) exercise. The compensatory hyperventilation phase reached during peak exercise implies increasing O_2 consumption due to respiratory effort. As the O_2 cost of ventilation increases, the ability to exercise at maximal work load decreases. This could explain the observed reduction in exercise time at peak exercise without a reduction in exercise when no compensatory hyperventilation is observed, and relatively more O_2 is available to exercising muscular tissue.

The results might suggest that β blockade improved aerobic efficiency because exercise time was reduced by 7% and peak $\dot{V}O_2$ reduced by 15%. However, there was no linear relation between these parameters and this postulate would be misleading. Work load and time increase linearly, whereas $\dot{V}O_2$ usually approaches a plateau during the final stages of exercise.

Beta blockade may affect the substrate for oxidative phosphorylation and influence respiration at the cellular level. Nonselective β blockade inhibits lipolysis, and increases the dependence of muscular tissue on glucose in relation to free fatty acids for substrate.[31] Increased oxidative catabolism of glucose will therefore give a higher respiratory quotient at the cellular level and this will raise the respiratory exchange ratio measured in expired air.

The chosen submaximal level of work defined at a respiratory exchange ratio of 1.00 can theoretically be influenced by changes in substrate. We therefore defined a submaximal work level corresponding to 60% of peak work load at first baseline. Placebo and timolol showed comparable respiratory exchange ratio values (0.98 ± 0.07 vs 0.98 ± 0.07) and a significant reduction in $\dot{V}O_2$ (17.2 ± 2.8 vs 15.9 ± 2.8, $p < 0.001$). Changes in substrate for oxidative catabolism do not appear to be important given the data in this study. This observation is also supported by another recent study.[32]

Gas exchange measurements during exercise provides objective, reproducible indexes of exercise performance. A submaximal exercise level corresponding to respiratory exchange ratio of 1.00 is easy to obtain, gives a reasonable prediction of peak $\dot{V}O_2$,[25] and corresponds well to the gas exchange anaerobic threshold.[20,33] The data obtained in this study demonstrate that nonselective β blockade substantially compromises functional capacity and reduces $\dot{V}O_2$ both at submaximal and peak exercise. The increased O_2 pulse only partially compensated for reduction in heart rate.

These findings are clinically relevant for a large patient population. The clinician prescribing β blockade for secondary prophylaxis should be aware of this pharmacologic reduction in exercise performance. Similarly, this effect should be taken into consideration when evaluating maximal exercise performance in patients participating in clinical research trials or rehabilitation programs. Small improvements in performance may well be masked or attenuated during concurrent β blockade.

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Effects of Acute K-Strophantidin Administration on Left Ventricular Relaxation and Filling Phase in Coronary Artery Disease

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In 10 patients with coronary artery disease, preserved left ventricular (LV) performance and absence of previous myocardial infarction, the effects of an acute intravenous administration of k-strophantidin (0.005 mg/kg over 10 minutes) on selected parameters of both LV systolic and diastolic function, including relaxation, were evaluated. An increase in positive first derivative of LV pressure (dP/dt) and in the ratio between dP/dt and the pressure developed (dP/dt/P) (1,530 ± 287) 1,600 ± 329 mm Hg/s [p <0.05], and 30 ± 6 to 34 ± 8 s^{-1} [p <0.05], respectively) demonstrated the inotropic effect of k-strophantidin, whereas volumetric parameters of systolic function (end-systolic and stroke volume indexes, and ejection fraction) did not show any significant change.

However, LV relaxation was impaired by k-strophantidin injection; in fact, mean values of T constant were significantly increased from 50 ± 12 to 55 ± 13 ms (p <0.01). Lowest LV and end-diastolic pressures increased from 8 ± 4 to 11 ± 4 mm Hg (p <0.05) and from 17 ± 6 to 20 ± 8 mm Hg (p <0.05), respectively. The end-diastolic volume and maximal rate of volumetric increase during the early and late filling phases were not modified by k-strophantidin. Mean aortic pressure increased from 110 ± 10 to 120 ± 12 mm Hg (p <0.001).

Therefore, in patients with coronary artery disease and LV preserved performance, an acute intravenous administration of k-strophantidin appears to stimulate contractility and to worsen relaxation, and minimal LV and end-diastolic pressures.

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The influence of drugs on the diastolic phase is a timely matter of cardiological interest, because diastolic dysfunction has been shown capable of producing cardiac illnesses, including heart failure, in spite of preserved systolic function. Although attention has long been focused on the relation between the effects of calcium antagonists[1–5] and β blockers[6–9] on the diastolic phase, the influence of inotropic agents on this phase has only recently been considered[10–13]; clinical data on this matter are poor, and, in particular, there are few studies on the effects of digitalis.[14,15]

In a previous study, we noted that an acute k-strophantidin injection in normal subjects[15] negatively influenced the course of the volumetric filling phase even if it did not modify left ventricular (LV) filling pressures. Recently in another study of patients with coronary artery disease (CAD) with previous myocardial infarction and preserved or mildly depressed ejection fraction we observed a more evident impairment of the LV filling phase (significant increase in end diastolic pressure) after k-strophantidin injection.[16] In order to explain this impairment we hypothesized a negative effect of k-strophantidin on LV relaxation.[16] Therefore, in the present study we proposed to study the diastolic phase, including relaxation after an acute intravenous k-strophantidin administration in patients with CAD, without previous myocardial infarction and altered ejection fraction.

METHODS

Ten patients (6 men and 4 women, aged 48 to 65 years, mean 57 ± 6) who underwent diagnostic cardiac catheterization for further evaluation of chest pain participated in the study. No patient had had myocardial infarction or presented features of heart failure, intraventricular conduction disturbances or valvular heart disease. All patients were in sinus rhythm and had a positive exercise test for ischemic heart disease. Patients with segmental LV dyskinetic area, abnormal volumes and thickness, and even mild alterations of left cardiac valvular function at echo-2-dimensional Doppler evaluation were excluded from the study.

After giving informed consent, patients underwent an invasive hemodynamic evaluation. All drugs were withheld ≥72 to 84 hours before the study, with the exception of nitrates that were withdrawn during the night before the first day of the study.

High-fidelity LV pressures were recorded using a Cordis-Sentron 7Fr microtip catheter (model 811/100) inserted through the femoral artery. LV angiography was performed through the same catheter. After recording the basal pressures, routine single-plane left ventric-

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TABLE I Angiographic Characteristics of the Patients

Case	Age (yr) & Sex	Ventriculography	Coronary Narrowing (% diameter ↓) LAD	LC	Right
1	48M	Normal	0	30	75
2	48F	Normal	90	0	30
3	52F	Normal	0	75	30
4	56F	Normal	50	0	75
5	57F	Normal	0	75	50
6	59M	Inferior hypokinesia	90	0	100
7	60M	Normal	50	95	0
8	61M	Normal	30	75	0
9	62M	Normal	95	30	30
10	65M	Lateral hypokinesia	90	50	0

LAD = left anterior descending; LC = left circumflex.

TABLE II Effects of an Acute Intravenous K-Strophantidin Administration on Pressure Variables

Parameters	B	A K-S	p Value
Lowest LV diastolic pressure (mm Hg)	8 ± 4	10 ± 4	<0.05
LV end-diastolic pressure (mm Hg)	17 ± 6	20 ± 8	<0.05
LV peak systolic pressure (mm Hg)	152 ± 16	159 ± 18	NS
Mean aortic pressure (mm Hg)	110 ± 10	120 ± 12	<0.001
Maximal rate of LV pressure increase during isovolumetric contraction (mm Hg/s)	1,530 ± 287	1,600 ± 329	<0.05
dP/dt divided by simultaneous developed pressure observed minus end-diastolic pressure (s^{-1})	30 ± 6	34 ± 8	<0.05
Maximal rate of LV pressure decrease (mm Hg/s)	1,629 ± 357	1,628 ± 334	NS
T constant (ms)	50 ± 12	55 ± 13	<0.01

A K-S = mean values ± standard deviation after k-strophantidin; B = mean basal values ± standard deviation; dP/dt = first derivative of LV pressure; LV = left ventricular; NS = not significant.

TABLE III Effects of an Acute Intravenous K-Strophantidin Administration on Volumetric Variables

Parameters	B	A K-S
End-diastolic volume index (ml/m^2)	76 ± 18	78 ± 19
End-systolic volume index ml/m^2)	26 ± 17	24 ± 19
Stroke volume index (ml/m^2)	50 ± 7	54 ± 6
Ejection fraction (%)	68 ± 12	71 ± 13
Maximal rate of volumetric increase during early filling phase (cm^3/sec)	0.47 ± 0.2	0.42 ± 0.1
Maximal rate of volumetric increase during late filling phase (cm^3/sec)	0.46 ± 0.1	0.43 ± 0.2

Abbreviations as in Table II.

ulography was performed with patients in the 30° right anterior oblique projection. To minimize hemodynamic changes due to contrast medium, patients remained in the recumbent position for 30 minutes after ventriculography. At this time, pressure values were not distinguishable from basal values, and thus, patients were injected with 0.005 mg/kg of k-strophantidin over 10 minutes. Pressure recordings were obtained again 30 minutes after the end of the k-strophantidin infusion. Thereafter, left ventriculography was repeated with the same dose of contrast medium (0.8 ml/kg of jopamidol)[17] used in the first cardiac angiography, and a selective coronary angiography was performed. Data were collected at a controlled heart rate achieved by atrial pacing (10 beats greater than spontaneous sinus rhythm) to obtain a reliably comparison of LV pressures and volumes before and after k-strophantidin administration.

Pressure data were recorded on an analogue tape recorder HP 3960 and were analyzed by an automatic procedure with an HP 2100 computer. Every reading of the pressure variables was obtained by averaging ≥9 consecutive beats.

Mean values (± standard deviation) before and after k-strophantidin were obtained for several calculated parameters: lowest LV and end-diastolic pressures; peak LV systolic pressure; mean aortic pressure, maximal rate of LV pressure increase during isovolumic contraction (positive dP/dt); maximal rate of LV pressure increase during isovolumic contraction divided by the simultaneous "developed" pressure observed minus end-diastolic pressure (dP/dt/P); maximal rate of LV pressure decrease during isovolumetric relaxation (negative dP/dt); time course of decrease of LV pressure (T constant);[18] end-diastolic, end-systolic and stroke volume indexes; ejection fraction; and maximal rate of volumetric increase during early and late filling phases. The latter 2 variables were assessed by calculating LV volumes every 20 ms from end-systole to end-diastole.[16]

Statistical analysis of the values obtained before and after k-strophantidin administration was performed with Wilcoxon signed rank test.

RESULTS

All patients were affected by a critical stenosis of ≥1 main coronary artery. LV wall motion was normal in 8 patients, whereas there was a segmental hypokinetic area in the remaining 2 (Table I). Overall LV kinesis was preserved in all patients (basal mean values of ejection fraction 68 ± 12).

Administration of k-strophantidin caused a stimulation of LV contractility evidenced by a significant increase of positive dP/dt and dP/dt/P (1,530 ± 287 to 1,600 ± 329 mm Hg/s [$p < 0.05$], and 30 ± 6 to 34 ± 8 s^{-1} [$p < 0.05$], respectively), whereas the volumetric variables of systolic function were not modified (Tables II and III).

On the contrary, a negative effect of k-strophantidin on the relaxation phase was observed. Even if the negative dP/dt did not change (Table II), the mean values of T constant increased significantly (50 ± 12 to 55 ± 13 ms; $p < 0.01$).

Furthermore, minimal LV and end-diastolic pressures were worsened by k-strophantidin administration,

the former being augmented from 8 ± 4 to 11 ± 4 mm Hg ($p < 0.05$), and the latter from 17 ± 6 to 20 ± 8 mm Hg ($p < 0.05$). LV peak systolic pressure did not change after k-strophantidin, whereas mean aortic pressure increased from 110 ± 10 to 120 ± 12 mm Hg ($p < 0.001$). LV volumetric variables, including maximal rate of volumetric increase during the early and late filling phases, showed small but not significant modifications (Table III).

Mean values ± standard deviation of the variables are listed in Tables II and III.

DISCUSSION

Digitalis substances, including k-strophantidin, are mainly known as positive inotropic agents. The increase of positive dP/dt and dP/dt/P in our patients demonstrates the inotropic effect of the acute intravenous administration of k-strophantidin. Volumetric variables such as end-systolic and stroke volume indexes, and ejection fraction did not show significant changes. This is not surprising, because pressure variables appear to be more sensible than volumetric parameters in evidencing modifications of the contractile state.[19] It should be mentioned that at therapeutical doses, digitalis glycosides exert a weak inotropic stimulation of normal myocardium.[20]

Despite the inotropic stimulation, LV performance does not appear to be improved in our patients. Therefore, adjustments of the other determinants of cardiac performance prevent this increase in contractility from being translated into an augmentation of cardiac performance. However, the diastolic phase appears to be impaired by k-strophantidin administration in our patients with CAD. In fact, we found an overt impairment of LV relaxation (lengthening of T constant from 50 ± 12 to 55 ± 13 ms; $p < 0.01$) after k-strophantidin. This finding is somewhat surprising, because the improvement in the contractile state should contribute to the increase in cardiac relaxation according to the concept of Gibson et al[21] that early relaxation is an active process energized by the preceding systole. However, it is possible that different inotropic stimulations do not necessarily have the same effects on the T constant. For example, T is increased in the postextrasystolic potentiated beat.[22] Clinical studies demonstrated the beneficial effects of some inotropic agents on both LV systolic and diastolic phases.[10,11,23] Previous experimental studies demonstrated that digitalis glycosides have no effects[14,24,25] on LV isovolumetric relaxation, even though negative actions on this phase have been shown by Lorell et al[26] in isolated ischemic rabbit hearts. There are no clinical studies available in the literature on the effects of digitalis on the relaxation phase. Our study provides the first data on this topic.

What are the mechanisms underlying the lengthening of relaxation after k-strophantidin in our patients with CAD?

Increased afterload, as it was observed in mean aortic pressure after k-strophantidin administration, could negatively influence LV isovolumetric relaxation phase by augmenting LV systolic load.[27] However, no linear correlation ($r = 0.04$) was observed between the lengthening of the T constant and the increase in mean aortic pressure. Furthermore, Little et al's[14] studies of dogs demonstrated that the effects of ouabain on T constant were not altered by LV unloading stimulation with propranolol or phentolamine pretreatment.

The stimulation of contractility caused by k-strophantidin increases the energetic expenditure of the left ventricle, which in the presence of ischemic heart disease may be compensated with an impairment of relaxation. However, in a previous study we reported that an acute intravenous administration of prenalterol dramatically improved both systolic and diastolic indexes, including relaxation in patients with CAD with previous myocardial infarction.[12]

Relaxation may be adversely affected by coronary vasoconstriction induced by digitalis glycosides. This phenomenon especially occurs when digitalis is administered as an acute intravenous bolus.[20] However, in our study k-strophantidin was administered slowly (injection lasted >10 minutes).

Finally, the negative effects of k-strophantidin on the relaxation phase in our patients with CAD may be related to its intrinsic mechanism of action at subcellular level. Digitalis substances are supposed to activate sodium-calcium transmembrane exchange through a sodium pump inhibition, thus elevating intracellular calcium.[28] This increased intracellular calcium availability stimulates contraction, but it may also reduce inactivation, which is an essential determinant of relaxation in intact hearts.[27] Furthermore, the remaining period of the diastolic phase was worsened by the acute k-strophantidin administration. Actually, volumetric variables did not change, whereas lowest LV and end-diastolic pressures significantly increased.

The pattern of the early and late filling phases was not significantly altered by k-strophantidin (Table III). Concerning the early filling phase, we suppose that left atrial pressure increased, because relaxation worsened and minimal diastolic pressure increased without changes in end-systolic volume. In this case, an increased left atrial pressure would maintain the same driving pressure between atrial and ventricular chambers as before k-strophantidin administration, because the transmitral gradient of pressure is the major determinant of the rapid filling phase.[22,29]

These data are in agreement with those obtained in a previous study where CAD patients with previous myocardial infarction and preserved or mildly depressed LV function were evaluated with an acute intravenous injection of k-strophantidin.[15,16]

The increase in filling pressure may, at least in part, be related to the negative effects of k-strophantidin on the relaxation phase. Nicolich et al[30] demonstrated that relaxation may influence filling pressure until the late diastolic period.

Our results provide evidence that digitalis glycosides may be disadvantageous in the treatment of subjects with intact systolic function.

Study limitations: Because we do not know how digitalis substances affect isovolumic relaxation in normal subjects it is uncertain whether the impairment of the relaxation phase observed in the present study is charac-

teristic of the patient clinical conditions (i.e., myocardial ischemia without previous myocardial infarction and altered systolic performance). However, our previous studies[15,16] of both normal subjects, and CAD patients with previous myocardial infarction and preserved or mildly depressed ejection fraction showed that an acute intravenous administration of k-strophantidin produces a negative influence on the LV filling phase. This phenomenon is known to be altered by an impaired relaxation.

Evaluation of coronary flow before and after k-strophantidin administration (not examined in the present work) in both normal and ischemic subjects may provide useful information on the intrinsic mechanisms by which digitalis substances produce negative influences on LV relaxation and filling pressures.

We cannot exclude that the basal ventriculography may have influenced the effects of k-strophantidin on the diastolic phase. However, this possibility is unlikely, because the effects of the drug on diastolic function were evaluated a long time (70 minutes) after contrast medium injection.

Our data were obtained after an acute intravenous administration of k-strophantidin; it is possible that a chronic administration of digitalis glycosides may produce different results.

Our data needs confirmation in a greater number of patients.

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Tissue Plasminogen Activator Using a Rapid-Infusion Low-Dose Regimen for Unstable Angina

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The clinical effect of a low-dose rapid-infusion intravenous regimen was assessed using human recombinant tissue-type plasminogen activator (rt-PA) in unstable angina. Fifty patients with unstable angina pectoris were randomly assigned to blinded treatment with either placebo (24 patients) or low-dose (20 mg bolus, 30 mg infusion over 1 hour) intravenous rt-PA (26 patients). Before randomization, all patients were treated with aspirin, twice-daily subcutaneous heparin, and maximally tolerated antianginal therapy. Of the 50 patients assigned, 26 received rt-PA and the outcome was successful in 15 (58%) (angina settled, no myocardial infarction or urgent intervention) compared with 9 (38%) successful outcomes in the 24 who received placebo (0.5 >p >0.1). Angina remained refractory in 8 (31%) of the rt-PA group and in 13 (54%) of the placebo group (0.1 >p >0.05). Urgent interventions were required in 6 patients (23%) who received rt-PA and in 11 patients (46%) who received placebo. Three patients in each group sustained a myocardial infarction within 72 hours of entering the trial and there were 3 deaths (1 in the active treatment group, 2 in placebo group) within 2 weeks of the trial (p = not significant). Administration of intravenous rt-PA was not associated with any complications. Low-dose rt-PA administration in patients with unstable angina was associated with a tendency to stabilization of anginal symptoms and a reduction in the need for urgent intervention. However, these trends did not achieve statistical significance.

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Unstable angina is a common manifestation of ischemic heart disease and progresses to acute myocardial infarction or sudden cardiac death in 10 to 15% of patients.[1,2] As with myocardial infarction, it appears that unstable angina is usually mediated by the superimposition of thrombus on an ulcerated, fixed atherosclerotic lesion.[3,4] Nonocclusive mural thrombi are present in 80% of patients with unstable angina compared with 21% of patients with acute myocardial infarction.[5]

Preliminary thrombolytic trials in unstable angina are encouraging.[6–10] The usual dosage regimen of intravenous recombinant tissue-type plasminogen activator (rt-PA) used for unstable angina has been similar to that used for acute myocardial infarction, i.e., 100 mg administered over 3 hours. There have been concerns as to the safety (cerebral bleeding), efficacy and convenience of administration of this regimen of rt-PA. This study evaluates the efficacy and safety of rapid-infusion, low-dose intravenous rt-PA to relieve the symptoms and reduce the need for urgent intervention in patients with unstable angina pectoris.

METHODS

Patient selection: Patients were eligible for the study if they were hospitalized with a recent exacerbation of typical angina pectoris and recurrent pain at rest or during minimal activity unresponsive to conventional medical therapy but without evidence of recent myocardial infarction. Patients were excluded if they had cardiomyopathy, valvular heart disease, recent bleeding, major trauma or had undergone surgery. Patients were also excluded if they had sustained a myocardial infarction within the last 2 weeks. Fifty patients were entered into the trial. The study was approved by the Hospital Ethics Committee and all patients gave written informed consent.

Study design: Patients were randomized to low-dose rt-PA (20 mg bolus followed by 30 mg intravenous infusion over 1 hour) or placebo in a double-blind fashion. Treatment was initiated within 72 hours of admission while the patients continued to receive maximum tolerated conventional antianginal therapy. Twenty-three patients (46%) were given a triple combination of nitrate (oral or transdermal), β-adrenoreceptor antagonist and calcium antagonist. All patients were treated with aspirin 300 mg/day, and low-dose (5,000 U twice daily) subcutaneous heparin. After completion of the infusion all patients were monitored continuously for recurrence of chest pain. If angina settled or returned to previous stable levels within 24 hours this was considered a successful end point. However, the outcome of the trial was

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TABLE I Comparison of Clinical Characteristics of Patients in the rt-PA and Placebo Groups

	rt-PA (n = 26)	Placebo (n = 24)
Age (year)	60 ± 11	62 ± 9
Men/women ratio	2:1	2:3
Current smokers (n) (%)	14 (54)	9 (38)
Remote myocardial infarction (n) (%)	9 (35)	13 (54)
Prior coronary artery bypass graft (n) (%)	6 (23)	7 (29)
Prior angioplasty (n) (%)	2 (8)	1 (4)
Duration of unstable angina (days)	10.7 ± 7.8	9.5 ± 7.2
Time from qualifying episode of pain to randomization (hours)	7.7	6.8
Medications before randomization (n) (%)		
Aspirin	26 (100)	24 (100)
Nitrate	15 (58)	14 (58)
β-adrenoreceptor antagonist	20 (77)	20 (83)
Calcium antagonist	22 (85)	22 (92)
Reversible ST depression* (n) (%)	18 (69)	13 (54)
Peak creatine kinase (mean) (U/liter)	103	72

*≥1 mm.
rt-PA = recombinant tissue-type plasminogen activator.

TABLE II Major Clinical Events Within Two Weeks of Randomization by Treatment Group

	rt-PA (n = 26)	Placebo (n = 24)
Angina at rest (n) (%)	8 (31)	13 (54)
Myocardial infarction (n) (%)	3 (12)	3 (13)
Urgent angiography (n) (%)	6 (23)	11 (46)
Emergency angioplasty (n) (%)	4 (15)	0
Urgent coronary artery bypass graft (n) (%)	1 (4)	6 (25)
Death (n) (%)	1 (4)	2 (8)
Myocardial infarction/ coronary artery bypass graft/angioplasty/death (n) (%)	9 (35)	11 (46)

rt-PA = recombinant tissue-type plasminogen activator.

considered to have failed if (1) unstable angina persisted or recurred requiring urgent coronary angiography, or (2) the patient developed acute myocardial infarction. The type of treatment was made available to all investigators 4 months after the completion of study.

Statistical analysis: The differences in incidence of successful and failed outcomes, persistence of refractory angina and the need for interventions in the 2 groups were compared by chi-square analysis. Student's *t* test was used to analyze the differences in left ventricular ejection fraction. Data are presented as mean ± standard deviation.

RESULTS

Fifty patients were randomized: 26 received rt-PA and 24 received placebo (Table I). There were more women (58%) in the placebo group but the rt-PA group was dominated by men (65%). Apart from the difference in gender and a higher incidence of remote myocardial infarction (54%) in the placebo group, the 2 groups were identical in all other respects. Eleven (42%) patients from the rt-PA group and 12 (50%) patients from the placebo group were taking a combination of nitrate, β-adrenoreceptor antagonist and calcium antagonist. All patients had ischemic chest pain; reversible electrocardiographic ST-segment changes were present in 18 (69%) of the rt-PA group and 13 (54%) of the placebo group. With the exclusion of patients who subsequently developed myocardial infarction, mean peak creatine kinase in the rt-PA group was 103 U/liter compared with 72 U/liter in the placebo group (normal <175 U/liter).

The outcome was regarded as successful if angina settled without a threefold increase in creatine kinase and the patient did not require urgent interventions in the form of coronary angiography, angioplasty or coronary artery bypass grafting. On this basis, of the 26 patients who were administered rt-PA, the outcome was successful in 15 (58%) compared with 9 (38%) successful outcomes in the 24 who were given placebo. However, the difference in successful outcomes did not achieve statistical significance ($0.5 > p > 0.1$). Angina at rest persisted or recurred in 8 patients (31%) from the rt-PA group and in 13 (54%) from the placebo group ($0.1 > p > 0.05$) (Table II). Three patients (12%) from the active group and 3 patients (13%) from the placebo group sustained myocardial infarction within 72 hours of entering the trial. Urgent coronary angiography was required in 6 patients (23%) who received rt-PA and in 11 patients (46%) who received placebo ($0.1 > p > 0.05$). Emergency angioplasty was required in 4 patients (15%) from the rt-PA group, whereas urgent coronary artery bypass grafting was required in 6 patients (25%) from the placebo group. There was 1 death in the rt-PA group and 2 deaths in the placebo group within 2 weeks of entering the trial.

Although urgent coronary angiography was required only if angina at rest persisted, angiographic data obtained within 4 months of entering the trial were available in 19 patients from each group. Mean left ventricular ejection fraction of the rt-PA group was 54 ± 17% and 60 ± 13% in the placebo group (p = not significant). Mean number of coronary arteries with significant (>75% narrowing) lesion in the rt-PA group (2.1 ± 0.7) was not significantly different from that in the placebo group (2.2 ± 1.2). No complications were observed that were ascribed to rt-PA.

DISCUSSION

The current medical treatment for unstable angina pectoris consists of combination therapy with nitrates, β-adrenoreceptor antagonists, calcium antagonists and antiplatelet agents.[11-15]

We have performed a prospective, randomized, placebo-controlled trial to study the effects of thrombolytic

therapy in patients with unstable angina refractory to standard treatment. We chose rt-PA for thrombolysis because of its clot specificity and a low-dose (50 mg) 1-hour infusion to reduce bleeding complications. Administration of rt-PA resulted in a tendency to a decrease in angina and the need for urgent intervention. There were more women in the placebo than in the rt-PA group, and the incidence of remote myocardial infarction was higher in this group. However we do not believe these differences accounted for the differing outcomes in the 2 groups. Although not all the patients in our study were taking triple antianginal therapy, the medications were optimized in all patients so that they were receiving maximum tolerated therapy.

The results of this study are in accordance with previous reports suggesting a beneficial effect of thrombolysis in unstable angina. Lawrence et al[16] studied intravenous streptokinase in patients with unstable angina and showed a significant reduction in the incidence of acute infarction and sudden death in the treated group. Gold et al[6] studied 24 patients with unstable angina taking maximal antianginal medications including intravenous heparin. Of the 12 patients receiving intravenous rt-PA (1.75 mg/kg) over 12 hours, unstable angina persisted in only 1 and lysis of intracoronary thrombi occurred in all 11 patients who consented to a coronary angiography. De Zwaan et al[7] showed that thrombolytic therapy (intracoronary streptokinase or intravenous rt-PA) administered to 41 patients a mean of 19 hours after their last episode of angina led to fewer patients with angiographic evidence of intracoronary thrombus. Before thrombolytic therapy was instituted, 68% of patients had evidence of intracoronary thrombus, compared with 39% after therapy. Topol et al[9] reported a significant increase in pacing thresholds to angina in 40 patients with angina at rest after rt-PA infusion without a comparable decrease in coronary stenosis. In a more recent study by Williams et al,[17] 67 patients with angina at rest received either low- or high-dose intravenous rt-PA or placebo in addition to oral aspirin and intravenous heparin. Mean coronary stenosis severity declined to a similar extent in each group. However, results only in the group taking low-dose rt-PA (0.75 mg/kg over 1 hour) achieved statistical significance. They concluded that a combination of intravenous rt-PA, aspirin and heparin was not clearly superior in reducing the severity of coronary stenosis in patients with unstable angina when compared with the combination of aspirin and heparin alone.

Similar to previous studies, we observed a lower incidence of adverse outcomes with rt-PA although statistical significance was not achieved. Taken together, this and previous studies strongly suggest a beneficial effect from thrombolytic therapy with a low incidence of adverse events. It has been clearly documented that aspirin is beneficial in unstable angina,[11,14] and because the patients in this and other studies were all taking aspirin, the benefit of thrombolysis appears to be an additive to the effect of aspirin. The efficacy of rt-PA may be enhanced by intravenous heparin; however, whether the administration of subcutaneous heparin may have influenced our results remains unclear.

The bleeding rate in previous studies using intravenous rt-PA has been between 43 and 66%,[6,17] often at puncture sites. No patient in our study experienced bleeding as a complication of low-dose rt-PA administration.

Overall, administration of low-dose rt-PA to patients with unstable angina was associated with a tendency to stabilization of anginal symptoms, and a reduction in the need for urgent intervention. However, these trends failed to achieve statistical significance.

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Effects of Estrogen Replacement Therapy on Serum Lipid Values and Angiographically Defined Coronary Artery Disease in Postmenopausal Women

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To examine the effects of estrogen replacement on lipids and angiographically defined coronary artery disease (CAD) in postmenopausal women, lipid profiles were obtained in 90 consecutive postmenopausal women undergoing diagnostic coronary angiography. Eighteen women (20%) were receiving estrogen and 72 (80%) were not. CAD (defined as ≥25% luminal diameter narrowing in a major coronary artery) was present in only 22% of women (4 of 18) receiving estrogen and in 68% (49 of 72) who were not ($p < 0.001$), with an odds ratio of 0.13. Mean high-density lipoprotein (HDL) cholesterol level was significantly higher (63 ± 6 vs 48 ± 2; $p < 0.01$) and mean total/HDL cholesterol ratio significantly lower in women receiving estrogen than in those who were not (4.2 ± 0.5 vs 5.1 ± 0.2; $p < 0.05$). The other lipid values were similar in both groups.

On multiple logistic regression analysis, absence of estrogen use was the most powerful independent predictor of the presence of CAD ($p < 0.001$), with total/HDL cholesterol ratio as the only other variable selected ($p < 0.01$).

Thus, among 90 consecutive postmenopausal women undergoing diagnostic coronary angiography, estrogen replacement therapy was associated with an 87% reduction in the prevalence of CAD, and those receiving estrogen had a significantly higher mean HDL cholesterol level and lower mean total/HDL cholesterol ratio.

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Coronary artery disease (CAD) is the leading cause of death in women.[1] However, CAD is rare in premenopausal women and occurs more often only in postmenopausal women.[2] This difference has been partly attributed to the cardioprotective effect of hormones in premenopausal women, and thus, it has been postulated that estrogen replacement therapy in postmenopausal women may confer cardioprotection.[3] Available studies examining the relation of estrogen to CAD reported conflicting data, with most showing substantial advantage,[3,4] others showing minimal effect,[5] and a few showing a disadvantage.[6] Furthermore, only a few studies have concurrently examined the effect of estrogen on lipid values and angiographically defined CAD.[7] This study reexamines the effects of estrogen replacement therapy on lipid values and angiographically documented CAD in postmenopausal women.

METHODS

Patient selection: The study group consisted of 90 consecutive postmenopausal women undergoing elective, diagnostic coronary angiography for evaluation of chest pain at Georgetown University Medical Center over an 8-month period, who had adequate visualization of both the left and right coronary arteries, and had a fasting lipid profile obtained the morning of the procedure. Menopause was defined as patients aged ≥55 years,[8] patient's affirmative response, or history of bilateral oophorectomy. Patients with recent myocardial infarction (<6 weeks before angiography), unstable angina, prior surgical or nonsurgical coronary revascularization, and those receiving lipid-lowering medications were excluded.

Coronary arteriography: Selective coronary arteriograms were obtained using either the Judkins or Sones technique and were independently reviewed by 2 cardiac radiologists without prior knowledge of the lipid values. Calipers were used to compare the diameter of a stenosed region with that of the nearest normal vessel. Stenoses were then classified as a percent reduction of the original diameter.

CAD was considered present if ≥1 major coronary artery system (left anterior descending, circumflex and right coronary artery) had a ≥25% stenosis. Left main disease was not analyzed separately, because only 8 women had left main involvement. When there was disagreement between the cardiac radiologists, the results were averaged.

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Lipid and lipoprotein measurements: Total cholesterol[9] and triglyceride[10] levels were determined using enzymatic hydrolysis with formation of hydrogen peroxide and subsequent measurement spectrophotometrically using reagents from Boehringer Mannheim Diagnostics (Indianapolis, Indiana) and the Hitachi 737 (Tokyo, Japan) chemistry analyzer. Apolipoprotein B-containing lipoproteins were precipitated with phosphotungstic acid and magnesium chloride and subsequent centrifugation according to the manufacturer's specifications (Boehringer).[11] High-density lipoprotein (HDL) cholesterol measurement was then performed on the supernatant. Low-density lipoprotein (LDL) cholesterol was in turn calculated using a modified Friedewald formula[12]: LDL cholesterol = total cholesterol − (HDL cholesterol + triglyceride × 0.16).

Risk factor assessment: Information on age, body mass index (kg/m^2), smoking (current smoker or former smoker stopped <2 years), hypertension and diabetes mellitus (both requiring treatment), family history of CAD (documented CAD in a first-degree relative aged <55 years [male] and <65 [female]), alcohol consumption (>1 drink/day), diet (adherence to low fat and cholesterol diet), exercise (>3 times weekly) and current use of medications (especially β blockers, diuretics and estrogens) that may influence serum lipid levels were obtained from medical records and by direct questioning of the patients.

Data analysis: Patients were grouped into those with CAD absent or present. Differences between mean age, lipid and lipoprotein values, and estrogen use between the groups were evaluated using Student's *t* test. Differences in categorical variables were measured using Fisher's exact test. Differences were considered significant for p values <0.05. Stepwise multiple logistic regression analysis was used to assess the independent contribution of each of the variables to the occurrence of coronary disease.

RESULTS

Patient characteristics: Clinical data for patients receiving or not receiving estrogen are listed in Table I. Baseline characteristics including mean age, body mass index and presence of traditional cardiac risk factors were different between the groups, but the differences did not reach statistical significance. The majority of the patients were not using concurrent progestin.

Lipid values: Mean total, LDL and HDL cholesterol, triglycerides (mg/dl) and total/HDL cholesterol ratio are shown in Table II. Mean HDL cholesterol level was significantly higher, and mean total/HDL cholesterol ratio was significantly lower in women receiving estrogen than in those not. Mean LDL cholesterol level was higher, and mean triglyceride level lower in women not receiving estrogen than in those who were; however, these differences did not reach statistical significance.

Presence of coronary artery disease: CAD was present in 4 of 18 (22%) women receiving estrogen compared with 49 of 72 (68%) who were not (p <0.001). Thus, estrogen use was associated with an odds ratio of 0.13 or with an 87% reduction in angiographic CAD. A stepwise multiple logistic regression model was constructed using age, body mass index, lipid parameters, presence of cardiac risk factors, and estrogen use as the independent variables to evaluate the effect of these factors on the occurrence of CAD. Absence of estrogen use was the most powerful independent variable related to the presence of CAD (p <0.001), with total/HDL cholesterol ratio as the only other variable selected (p <0.01).

TABLE I Characteristics of Study Groups

	Estrogen (n = 18)	No Estrogen (n = 72)	Odds Ratio	p Value
Age (yr)	58 ± 8	63 ± 8	NA	NS
Body mass index (kg/m^2)	25 ± 4	27 ± 8	NA	NS
Risk factors				
Hypertension	6 (33%)	39 (54%)	0.42	NS
Diabetes mellitus	1 (5%)	20 (28%)	0.15	NS
Smoking	1 (5%)	16 (22%)	0.21	NS
Family history	8 (44%)	17 (23%)	2.59	NS
Myocardial infarction	1 (5%)	11 (15%)	0.33	NS
Low fat and cholesterol diet	9 (50%)	27 (38%)	1.67	NS
Exercise	6 (33%)	11 (15%)	2.77	NS
Alcohol use	1 (5%)	7 (10%)	0.55	NS
β-blocker use	2 (11%)	20 (28%)	0.33	NS

Values for age and body mass index are mean ± standard deviation.
NA = not applicable; NS = not significant.

TABLE II Mean Lipid Values of Study Groups

	Estrogen (n = 18)	No Estrogen (n = 72)
Total cholesterol (mg/dl)	225 ± 51	222 ± 42
Low-density lipoprotein cholesterol (mg/dl)	131 ± 42	151 ± 42
High-density lipoprotein cholesterol (mg/dl)	63 ± 25	48 ± 17*
Triglycerides (mg/dl)	165 ± 144	147 ± 42
Total/high-density lipoprotein cholesterol	4.2 ± 0.5	5.1 ± 0.2**

*p <0.01; **p <0.05 vs estrogen group.
Values are mean ± standard deviation.

DISCUSSION

The results of this study indicate that among postmenopausal women undergoing diagnostic coronary angiography for suspected CAD, estrogen use was associated with an 87% reduction in angiographic prevalence of CAD, and those receiving estrogen had a significantly higher mean HDL cholesterol level and lower mean total/HDL cholesterol ratio than did those not receiving estrogen. Furthermore, on multiple logistic regression analysis, estrogen use, followed only by total/HDL cholesterol ratio, was the most powerful predictor of the presence of CAD in these women.

Previous angiographic studies reported a reduction in the incidence of angiographic CAD in women receiving estrogen.[7,13,14] Studies that have concurrently correlated estrogen use to lipid values showed a significantly higher HDL cholesterol level in women receiving estrogen.[7]

Our definition of CAD needs explanation. Recent studies have suggested that plaques producing only mild to moderate angiographic luminal stenosis constitute

the majority of those undergoing abrupt rupture, resulting in acute ischemic syndromes,[15] and that the initial angiographic severity of coronary stenoses does not predict the time or location of subsequent coronary occlusion.[16] Coronary vasomotor studies showed that even angiographically normal-appearing coronary segments in patients with CAD may have diffuse endothelial dysfunction, indicating early atherosclerosis that is not yet detectable by angiography.[17] Thus, we chose our definition of CAD as ≥25% luminal diameter narrowing to identify patients with early but not necessarily clinically significant atherosclerosis.

Postulated mechanisms: One likely mechanism involves the favorable effect of estrogen on lipid values. Recent studies reported that a high HDL cholesterol level may confer an independent cardioprotection.[18] Furthermore, as we showed recently, the resultant lower total/HDL cholesterol ratio from estrogen therapy would decrease the likelihood of angiographic CAD in postmenopausal women.[19] Other possible mechanisms include estrogen's effect on carbohydrate metabolism[20] and blood pressure.[21] Furthermore, in animal studies estrogen modulates the vasoconstrictor responses of atherosclerotic coronary arteries,[22] inhibits cell proliferation after endothelial injury, and stimulates prostacyclin biosynthetic activity.[23]

Need for preventing coronary artery disease in women: Although CAD occurs about a decade later in women than in men and is infrequent in premenopausal women, women with overt CAD have a worse prognosis than do men. Women, especially black women with myocardial infarction, have increased morbidity and mortality compared with those of men.[24] Surgical and nonsurgical revascularization is also less successful in women.[25,26] Recent regression studies suggest that it is possible to reverse the atherosclerotic process.[27] Thus, it is essential to identify interventions in women that would prevent the development of CAD.

Study limitations: There was a small number of women receiving estrogen in our study, possibly because estrogen therapy protects them from CAD and because few of them receiving estrogen have symptoms suggestive of CAD and require coronary angiography. Thus, this small number of women receiving estrogen may preclude the ability to detect any significant differences in baseline characteristics between the groups. There may be a difficulty in recalling the exact age of menopause, especially for more elderly patients. Only 1 set of lipid measurements was obtained from each patient, although recent studies suggest that there can be significant day-to-day variability of serum lipid levels[28] and wide within-person fluctuations.[29] Because our patients were preselected for coronary angiography, they are neither a representative sample of postmenopausal women in the general population, nor that of women with CAD.

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Patterns of Referral and Recovery in Women and Men Undergoing Coronary Artery Bypass Grafting

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This study compares women and men undergoing coronary artery bypass grafting. Factors before and after coronary surgery were examined to identify variables related to mortality and morbidity. The study population included 465 women and 465 men matched for age (mean age 64.2 years) who underwent first time isolated coronary artery bypass grafting between 1983 and 1988. There were higher incidences of systemic hypertension, diabetes mellitus, postmyocardial infarction angina, thyroid gland disease, arthritis ($p < 0.001$ for all), acute myocardial infarction ($p = 0.03$), congestive heart failure ($p = 0.03$), and emergency surgery ($p = 0.02$) in women, whereas more men had peptic ulcer disease ($p < 0.001$). The in-hospital death rate was not significantly different (women 4.3% vs men 3.7%). For all subjects, emergency surgery ($p < 0.001$), significant left main narrowing ($p < 0.05$) and renal disease ($p < 0.001$) were related to death, whereas history of myocardial infarction ($p < 0.05$) and diabetes ($p < 0.05$) were related to death only in men. Age and body surface area were not related to death. After surgery men had a higher incidence of atrial arrhythmia ($p < 0.001$), and women had a higher incidence of congestive heart failure ($p < 0.001$). Although women did not have a higher mortality rate, the data suggest that women and men do not share all the same predictors of mortality after surgery.

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Although it is generally believed in clinical practice that women undergoing coronary artery bypass grafting (CABG) have a higher risk of mortality and morbidity, research data addressing these assumptions are equivocal. Some investigators reported higher mortality rates for women,[1–4] whereas others reported equal rates for women and men, particularly if the rates were adjusted for body size, diameter of the grafted vessel, and age.[5–8] In a review of studies comparing men and women undergoing CABG, data indicated that although women who underwent CABG were generally at higher risk in terms of their symptoms and comorbidities, they were at lower risk in terms of the extent of coronary artery disease and evidence of prior myocardial damage.[9] Recent reports suggested that different criteria are used in referring women for surgery,[10,11] which possibly accounts for the increased risk of operative death.[12] The purpose of the present study was to characterize preoperative status in a group of women undergoing CABG compared with that in an equal number of age-matched men, and to identify relations between factors before and after coronary surgery.

METHODS

Study population: All women who had first time CABG between 1983 and 1988 at 1 medical center were included in the study. Women who had any other cardiac surgical procedure in addition to CABG were excluded. For each woman included in the study, 1 man matched for age, year of surgery, and having undergone first time isolated CABG was randomly selected from a computer-generated list of all patients with CABG at the medical center. The study consisted of 465 women and 465 age-matched men.

Data collection: The hospital record of each subject was reviewed using a standard data collection form by 2 trained chart reviewers. Demographic data, presence of preexisting comorbidities, risk factors and medications at admission and discharge were obtained from the nursing and medical histories. Perioperative data were collected from operation room reports. Body surface area of each subject was computed from weight and height using the Dubos formula.[13] Indicators of postoperative recovery and complications were identified by detailed review of the progress notes. Mortality was defined as death occurring during the hospitalization in which surgery took place. Access to hospital records was approved by the university human subjects review board.

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TABLE I Comparison of Factors Before Surgery

	Women (%) (n = 465)	Men (%) (n = 465)	p Value
Risk factors before surgery			
Systemic hypertension	296 (63.7)	234 (50.3)	<0.001
Diabetes mellitus	109 (23.4)	61 (13.1)	<0.001
Myocardial infarction (occurence)			0.689
Documented MI	249 (53.7)	256 (55.3)	
Silent MI	56 (12.2)	59 (12.3)	
MI (type)			0.026
Old MI	245 (52.8)	277 (59.8)	
Acute MI	60 (12.9)	38 (8.2)	
Postmyocardial infarction angina	71 (15.3)	35 (7.5)	<0.001
Congestive heart failure	101 (21.9)	75 (16.1)	0.030
Emergency surgery	35 (7.5)	17 (3.7)	0.015
Left main narrowing	76 (16.3)	83 (17.8)	0.591
Smoking history	248 (53.9)	340 (73.9)	<0.001
Other comorbidities			
Thyroid gland disease	48 (10.3)	7 (1.5)	<0.001
Arthritis	108 (23.2)	66 (14.2)	<0.001
Peptic ulcer	18 (3.9)	49 (10.5)	<0.001
Pulmonary disease	41 (8.8)	50 (10.8)	0.383
Renal disease	27 (5.8)	25 (5.4)	0.880
Peripheral vascular disease	72 (15.5)	67 (14.4)	0.703
Hiatal hernia	47 (10.1)	34 (7.3)	0.160

MI = myocardial infarction.

Analyses: Paired samples *t* tests were used for univariate analyses of continuous variables in testing for differences between women and men. For categorical data, chi-square analysis was used, with the continuity correction for chi-square computed when appropriate. Multivariate comparisons to test for relations of preoperative factors with mortality were performed using the logistic regression model. To test for main effects of preoperative variables on mortality, these variables were entered into the logistical regression equation first as a simultaneous set. In a second step, a set of variables representing the interaction terms of each preoperative factor with sex were entered into the equation to detect if different variables were related to mortality for women or for men. Standard multiple regression technique was used in analyses where body surface area was the dependent variable. All data analyses were performed using the Statistical Package for the Social Sciences.[14]

RESULTS

Mean age of the women (men were matched for age) was 64.2 years (range 30 to 84). The proportion of women aged >65 years, significantly increased from 37% in 1983 to 60% in 1988 (p = 0.025). The patients were predominantly white (97%). Fewer women than men were married (57 vs 88%; p <0.001), with most single women being widowed (29%).

Preoperative factors: In general, women had higher incidences of cardiac-related risk factors than did men (Table I). There was no difference between women and men in total incidence of myocardial infarction; however, women had a higher incidence of acute myocardial infarction. There were fewer differences between women and men for noncardiac-related comorbidities. The incidence of comorbidities was congruent with the medications prescribed for subjects before surgery. More women than men were being treated with antihypertensives, hypoglycemics, a combination of digoxin or diuretics, or both, thyroid supplements and antiinflammatory agents. The only difference in medication prescribed before surgery that was not congruent with comorbidity was that more women were treated with antianxiety medication (19 vs 12%; p = 0.003).

TABLE II Comparison of Baseline and Operative Factors

	Women (n = 465)*†	Men (n = 465)*†	p Value
Height (cm)	158.9 ± 6.7	172.4 ± 7.2	<0.001
Weight (kg)	69.5 ± 13.5	82.6 ± 12.9	<0.001
Body surface area (m^2)	1.7 ± 0.2	2.0 ± 0.2	<0.001
Number of anastomoses	3.0 ± 1.0	3.4 ± 1.0	<0.001
Pump time (mins)	91.5 ± 29.2	101.0 ± 28.6	<0.001
Ischemic time (mins)	53.2 ± 19.7	61.7 ± 19.9	<0.001
Cardiac index	2.3 ± 0.6	2.4 ± 0.5	0.022

* Cardiac index based on n = 450.
†Values are mean ± standard deviation.

Operative factors: Women were significantly smaller then men, and had fewer distal anastomoses and shorter total cardiopulmonary bypass and myocardial ischemic times (Table II). Body surface area and ischemic time were positively correlated (r = 0.15; p < 0.01). Controlling for number of anastomoses, the semiparital (unique) correlation between body surface area and ischemic time was substantially reduced (sr = 0.003; p <0.01), indicating that the number of anastomoses rather than body size influenced ischemic time while on cardiopulmonary bypass.

Mortality: The in-hospital death rates were 4.3% for women (n= 20) and 3.7% for men (n = 17) (p = 0.613). There was no difference between women and men in the proportion of intraoperative (30 vs 29%) to total deaths. The primary cause of death in 70% of women and 71% of men was cardiac failure. Using logistic regression analysis, factors before surgery found to be related to mortality for all subjects were emergency surgery (p <0.001), and left main (p <0.05) and renal (p <0.001) diseases. Significant interaction terms indicated that history of myocardial infarction (p <0.05) and diabetes (p <0.05) were related to death only in men. Age and body surface area were not related to death.

Complications after surgery: There were few significant differences between women and men in incidences of complications after surgery (Table III). When psychological deficits were noted, women's deficits were about equally attributed to confusion and emotional upset, whereas men's deficits were almost always attributed to confusion (p = 0.016). The occurrence of complications after surgery was congruent with the medica-

tions prescribed at discharge from the hospital. More men were treated with antiarrhythmic agents, whereas more women were treated with a combination of digoxin or diuretics, or both, and antianxiety agents.

DISCUSSION

This study was limited in that the sample was homogeneous for race, thus restricting the scope of the findings. In addition data regarding ventricular ejection fraction was not available, and interpretations of data regarding incidence of congestive heart failure after surgery must be viewed in that light.

In the current series there was no difference in mortality rates between women and men matched for age. Our mortality rate for women (4.3%) was comparable to that reported by Khan et al (4.6%).[12] These findings are consistent with reports[5–9] in which age rather than gender explained higher in-hospital mortality rates in women after CABG. However, factors previously hypothesized to place women at greater risk, such as higher incidences of hypertension, diabetes and congestive heart failure,[15] were not related to mortality for women in this study. Khan reported hypertension and history of myocardial infarction to be significantly related to mortality; however, by testing for interactions between factors before surgery and gender we found that history of myocardial infarction was related to mortality only in men. Left ventricular function before surgery was previously shown to be related to mortality after CABG.[8] However, Tofler et al[16] demonstrated that with comparable infarct size and history of myocardial infarction women have a higher left ventricular ejection fraction after infarction than do men. It may be that prior myocardial infarction is a better surrogate of left ventricular function in men than in women, and thus predicts outcome in men. We also found that diabetes was related to mortality in only men. These findings indicate that the predictors of mortality for women are different from those for men.

Before surgery, more women than men were being treated with antianxiety medication. After surgery, women's psychological symptoms were more likely to be interpreted as emotionally based and treated with psychotropic drugs, whereas men's psychological symptoms were more likely to be interpreted as organically based. These results lend some support to the notion that symptoms may be interpreted differently for women and men. However, the data must be viewed with caution, because the number of cases in the subgroups are small and because documentation of psychological events in hospital records may be biased.

Our data did not demonstrate any significant effect of body surface area on in-hospital mortality, which was consistent with other reports.[6,12] Though ischemic and pump times were shorter for women, when the number of anastomoses was statistically controlled, the correlation between body surface area and ischemic time became negligible. This result, as well as the finding of no difference in mortality between women and age-matched men, argues against the concept that technical difficulties with anastomoses are related to smaller body surface area. Khan et al[12] argued that discrepancies among earlier reports on the relation between body surface area and mortality may be due to the current use of perioperative antiplatelet agents and improved operative techniques, thus eliminating increased mortality associated with smaller body size. They also suggested that in the older population of patients currently undergoing coronary artery surgery, body size may not be significantly related to mortality. We concur with these speculations and add that body surface area may not be a good correlate to coronary artery size in an older population.

TABLE III Comparison of Complications After Surgery

	Women (%) (n = 459)*	Men (%) (n = 460)*	p Value
Reoperation	16 (3.4)	29 (6.2)	0.067
Perioperative MI	31 (6.7)	23 (4.9)	0.322
Postoperative MI	12 (2.6)	8 (1.7)	0.491
Atrial arrhythmia	119 (25.6)	170 (36.3)	<0.001
Ventricular arrhythmia	35 (7.5)	49 (10.5)	0.137
Pulmonary insufficiency	51 (11.0)	47 (10.1)	0.838
Renal insufficiency	12 (2.6)	12 (2.6)	1.000
Incisional infection	46 (9.9)	42 (9.0)	0.737
Neurological			0.594
CVA	6 (1.3)	3 (0.6)	
Non-CVA deficit	13 (2.8)	14 (3.0)	
Psychological			0.016
Confusion	15 (3.2)	26 (5.6)	
Emotional upset	10 (2.2)	2 (0.4)	
Congestive heart failure	43 (9.2)	17 (3.7)	<0.001
Pericarditis	8 (1.7)	6 (1.3)	0.788
Angina	6 (1.3)	2 (0.4)	0.287

*Excludes intraoperative deaths.
CVA = cerebrovascular accident; MI = myocardial infarction.

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Comparison Between Thallium-201 and Technetium-99m Methoxyisobutyl Isonitrile Defect Size in Single-Photon Emission Computed Tomography at Rest, Exercise and Redistribution in Coronary Artery Disease

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Defect size on myocardial tomograms was measured in 30 patients who underwent 2 separate studies, 1 with thallium-201 (Tl-201), the other with technetium-99m-methoxyisobutyl isonitrile (MIBI). A group of 15 patients with myocardial infarction was studied at rest and received both tracers on the same day. The other 15 patients had documented coronary artery disease. They were were given injections of Tl-201 at peak exercise and underwent imaging immediately after exercise and again 4 hours later. They then received a dose of MIBI for imaging at rest. A week later they underwent a second exercise test with the same work load and received a second dose of MIBI. Defect size on single-photon emission computed tomographic images was measured and repeated twice. Results were expressed in percentage of the volume of the whole myocardium.

Reproducibility of the defect size measurement was high for Tl-201 ($r = 0.978$; SEE = 1.59) as well as for MIBI ($r = 0.981$; SEE = 0.80). In patients with coronary artery disease the mean size of the defects was significantly larger with Tl-201 than with MIBI at exercise (6.7 ± 5.2 vs 4.6 ± 5.2%, respectively, $p < 0.05$) and at redistribution (5.1 ± 4.4 vs 2.8 ± 3.2%, respectively, $p < 0.05$), where no difference was seen in patients with myocardial infarction studied only at rest (11.2 ± 10.4 vs 12.0 ± 11.5%, respectively, p = not significant).

Smaller MIBI defect sizes, when compared with Tl-201, in the exercise and redistribution studies were not due to technical artefacts since there was no difference when they were compared at rest.

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Technetium-99m-methoxyisobutylisonitrile(MIBI) is now an alternative to thallium-201 (Tl-201) for myocardial infarction imaging.[1,2] Its more favorable physical properties allow one to administer higher doses than with Tl-201, resulting in images of higher quality.[3] Because of its slow redistribution, images of the initial tracer distribution in the myocardium can be acquired for up to several hours after injection.[4,5]

Although many experimental studies have demonstrated that both tracers distribute grossly in the myocardium as a function of coronary blood flow,[6,7] several studies have also shown that their tissular and cellular uptakes are partly controlled by active, but different, processes.[8–14]

In the detection of coronary artery disease, the sensitivity of MIBI single-photon emission computed tomography (SPECT) imaging has been shown to be close to Tl-201,[1,2,15] although it was never demonstrated to be significantly superior. Morever, it has been found that, at exercise, mean size of the MIBI defects measured by a semiautomatic method is smaller than the mean size obtained with Tl-201.[16] To test whether this difference (1) could be observed with a different method of defect size measurement, (2) could be explained by the differences in the quality of Tl-201 and MIBI images, or (3) was due to differences in the myocardial uptake of these tracers, we evaluated 2 groups of patients with Tl-201 and MIBI. In 1 group, all patients had presented with a myocardial infarction and were studied at rest. The other group included patients with coronary artery disease who were studied at exercise and redistribution. A difference in the defect size measured on the MIBI and Tl-201 images in the group with myocardial infarction would most likely result from differences in the image qualities between the 2 agents, since their delivery to the chronically blood flow–deprived area should be impaired in a similar fashion. On the contrary, a lack of difference would demonstrate that defect size measurement is not affected by the unequal imaging qualities of MIBI and Tl-201. In that case, if differences in the Tl-201 and MIBI defect size were observed at exercise or redistribution/rest studies in the group of patients with coronary artery disease, this could be explained only by differences in the myocardial distribution of the tracers in conditions of rapidly reversible ischemia.

METHODS

Patients: The first group included 15 patients of whom 1 was a woman (age range 35 to 80 years). All had presented with an acute myocardial infarction evidenced by enzymatic and electrical data.

The second group of 15 patients involved 13 men and 2 women (age range 36 to 67 years). All patients had undergone contrast coronary angiography within 3 weeks of the scintigraphic studies. Five patients had significant lesions (stenosis >70% diameter) only in the left coronary artery, 6 only in the right artery, 3 in both arteries, and 1 patient had no significant coronary stenosis. Four patients had a documented myocardial infarction.

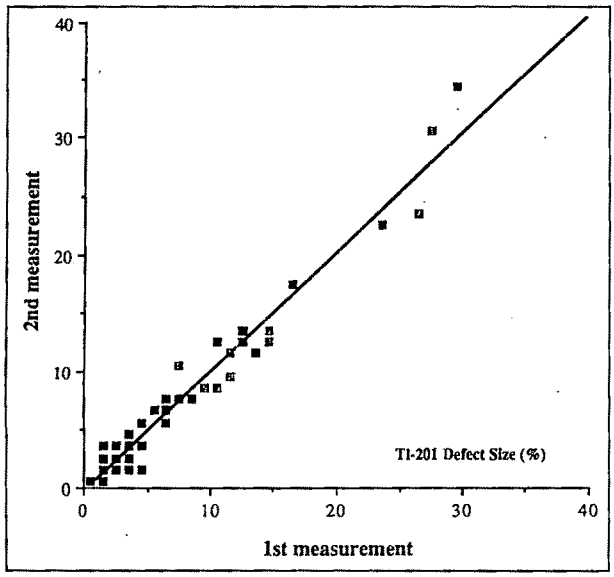


FIGURE 1. Reproducibility of the measurement of the defect size on thallium-201 (Tl-201) myocardial sections in 15 patients with a myocardial infarct who were studied at rest, and in 15 with coronary artery disease studied at exercise and redistribution. These 45 paired values yielded a correlation coefficient of 0.98. The equation of the regression line is $y = -0.29 + 1.03x$. SEE = 1.59%.

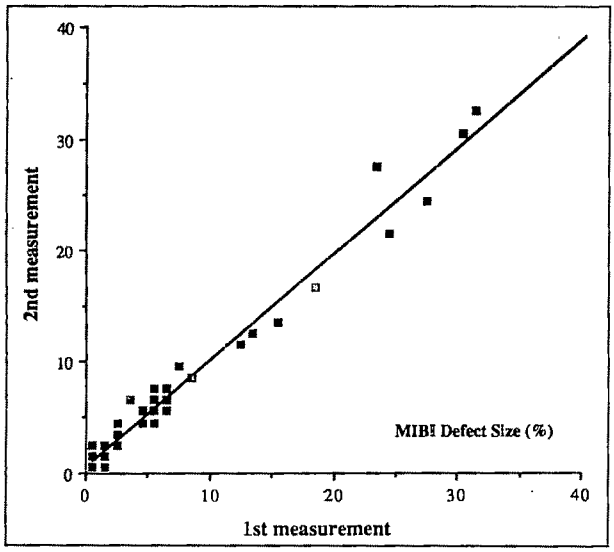


FIGURE 2. Reproducibility of the measurement of the defect size on methoxyisobutyl isonitrile (MIBI) myocardial sections in 15 patients with a myocardial infarct who were studied at rest, and in 15 with coronary artery disease studied at rest and at exercise. These 45 paired values yielded correlation coefficient of 0.99. The equation of the regression line is $y = 0.56 + 0.95x$. SEE = 1.38%.

All patients gave their informed consent to the protocol in accordance with the rules of the local Human Subjects Committee.

Protocol and data acquisition: In the group with myocardial infarction, each patient received at rest a 111 kBq (30 μCi)/(kg of weight) dose of Tl-201 chloride (Oris, Saclay, France). Imaging was begun within the next 10 minutes using a 40 cm diameter rotating scintillation camera (Gammatome 2, Sopha, Buc, France) equipped with a parallel-hole, general-purpose collimator. The spectrometry was set on the 69 to 83 keV x-ray emission of Tl-201 with a 25% window. A series of 32 planar views of 30 seconds each were acquired in a step-by-step mode between the left posterior and right anterior oblique projections. After completion of the image acquisition phase, each patient received a 740 MBq (20 mCi) dose of MIBI. Imaging was started 1 hour later with the same conditions, except that spectrometry was set on the 140 keV gamma-ray emission of technetium-99m (Tc-99m) with a 20% window.

In the group with coronary artery disease, the patients underwent a symptom-limited exercise test on a bicycle using work load steps of 25 W every minute. A 740 MBq (20 mCi) dose of MIBI was injected at 1 minute before termination of exercise. Imaging was performed 1 hour later with the conditions as described.

One week later, these patients exercised using exactly the same duration and work load as the week before. They received a dose of Tl-201 at peak exercise. Imaging was performed within 5 minutes using the same imaging protocol as that for the Tl-201 studies at rest. Four hours later, during the redistribution phase, these patients underwent imaging at rest using an acquisition duration of 40 seconds per projection. They then received a 740 MBq (20 mCi) dose of MIBI at rest. One hour later imaging was performed under the same conditions as the week before.

Image processing: The series of 32 projection views were stored on 64 × 64 matrixes in a dedicated computer (Simis 5, Sopha, Buc, France). Each series was used for reconstruction of transverse tomographic sections by the standard back projection algorithm available in the computer. A pure ramp filter was selected. There was no correction for depth attenuation or scatter diffusion. After reconstruction, the series of 1-pixel-thick parallel transverse sections cutting through the heart were submitted to a tridimensional isotropic filtering. This smoothing process averages the value of each pixel with the weighted values of its 18 nearest neighbors: 8 in the same section, 5 in the upper and 5 in the lower sections, respectively. A series of sagittal sections were then reconstructed by rearrangement of the lines and columns in the transverse sections. Finally, the 2 series of sections were enlarged by a factor of 2.

Defect size was measured using a method formerly validated in an animal model[17] and in a patient study.[18] In brief, the transverse plane is retained for processing if

the defect is mostly septal, anterior or lateral. Otherwise, only the sagittal sections are processed. Once the appropriate plane has been selected by the operator, a rectangular region of interest is positioned outside the limits of the thorax on the central section of the series. The mean count activity, assumed to represent the reconstruction background activity, is substracted from the activity of all the pixels of the series. Then the maximum activity in the series is calculated and the level corresponding to 35% of its value is set as the limit between the normal and infarcted cardiac tissue. The sections are then displayed 1 by 1 on a monitor, with a line showing this level of activity. With the help of a cursor appearing on the monitor, the operator manually draws the endocardial and epicardial limits of the defect. Once this has been completed on the series of transverse or sagittal sections, the surface of the areas of normal and abnormal tissue is calculated. This summation corresponds to the volume of these areas. The abnormal area is expressed in percentage of the overall myocardial volume, since it was found to provide the best correlation with pathologic data in an animal model.[17]

All measurements were performed twice by the same operator, with several days between the 2 processes. The final result was the average of these 2 values.

Statistics: Results are presented as mean ± standard deviation. Comparisons were done using the Student's *t* test for paired data. Regression analysis ($y = ax + b$), correlation coefficients (r) and standard errors of the estimate were calculated using standard formulas.

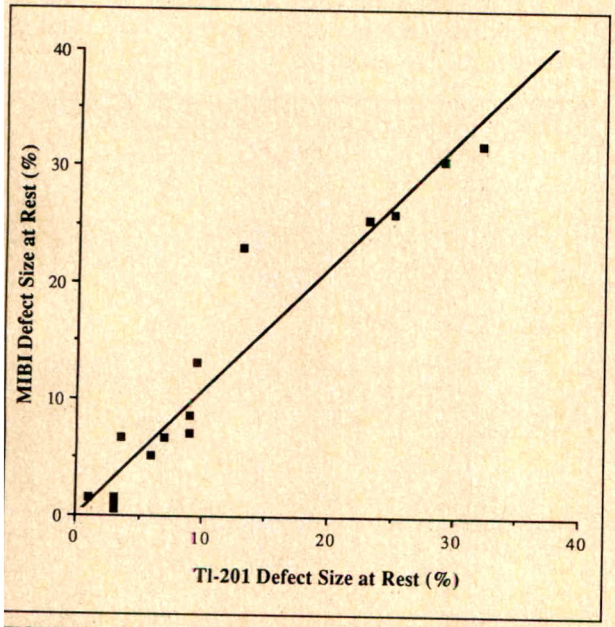


FIGURE 3. Comparison between the myocardial defect size measured by thallium-201 (Tl-201) and methoxyisobutyl isonitrile (MIBI) single-photon emission computed tomography in 15 patients presenting with a myocardial infarction and studied at rest. The agreement was good (r = 0.964, SEE = 3.2%), suggesting that despite differences in the injected activities (2 mCi for Tl-201 and 20 mCi for MIBI) and energy of radiation emissions (69 to 73 keV for Tl-201 and 140 keV for MIBI) the method used for the defect size measurement is not significantly influenced by such differences.

RESULTS

Exercise testing: Maximal heart rate and maximal double product during exercise were not significantly different between the first (130 ± 15 and 23,900 ± 4,600, respectively) and second (131 ± 15 and 24,500 ± 5,000) exercise test. Beta-blocker therapy was discontinued in all patients for at least 5 half-lives of the drug, when necessary.

Reproducibility of defect size measurement: Results of the repeated measurements of defect size with Tl-201 and MIBI are shown in Figures 1 and 2, respectively. Reproducibility was not different between the 2 tracers (r = 0.978 for Tl-201 and r = 0.986 for MIBI). SEE was also comparable (1.59 and 1.38%, respectively).

Estimates of defect size: Figure 3 shows that there was a good agreement between the Tl-201 and MIBI defect size measurement in the group of patients presenting with a myocardial infarction and studied at rest. The difference in the defect size was not significant (11.2 ± 10.4% for Tl-201 and 12.0 ± 11.5% for MIBI).

In the group of patients with coronary artery disease, a significant difference was observed at exercise (6.7 ± 5.2% for Tl-201 and 4.6 ± 5.2% for MIBI, $p < 0.05$) and at redistribution or rest (5.1 ± 4.4% for Tl-201 at redistribution and 2.8 ± 3.2% for MIBI at rest, $p < 0.05$). Figures 4 and 5 show that the correlations between Tl-201 and MIBI were also weaker than in the former group of patients.

DISCUSSION

Results demonstrate a lack of difference between defect size measured with the 2 tracers in the studies at rest performed in patients with myocardial infarction,

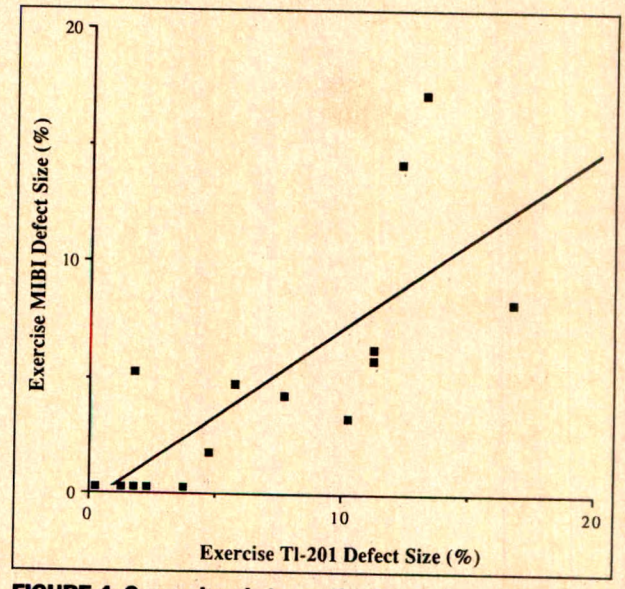


FIGURE 4. Comparison between the defect size measured on single-photon emission computed tomographic images with thallium-201 (Tl-201) and methoxyisobutyl isonitrile (MIBI) in 15 patients presenting with documented coronary artery disease who underwent imaging after a tracer injection at peak exercise. Regression analysis yielded the following values: y = −0.47 + 0.75x, r = 0.76; SEE = 3.5%. These results demonstrate a clear underestimation of the defect size with MIBI, although in a few patients the reverse could be observed.

whereas there was a significant underestimation of the mean defect size with MIBI in patients with coronary artery disease. In the latter, the correlation between Tl-201 and MIBI became weak, some defects being even bigger with MIBI than with Tl-201. Globally, the MIBI underestimation in defect size was observed at exercise as well as at rest/redistribution. The relative variation between exercise and redistribution or rest was higher for the MIBI studies than for the Tl-201 studies (35% change for MIBI, and 24% for Tl-201), although it was nearly similar when expressed in defect size units (1.8 vs 1.6, respectively). Reproducibility of the method was good, although reproducibility of exercise-induced defects using the same radioisotope in repeated studies was not evaluated.

Because of differences between the count statistics as well as between the energy of emission of Tl-201 and Tc-99m, differences between defect size measured on single-photon emission computed tomographic images could be expected. In effect, because of their different physical and biological properties, Tl-201 and MIBI are injected at different doses and the resulting count statistics collected in the scintigraphic images are more favorable with Tc-99m (ratio 5/1). However, we have observed no significant difference between the Tl-201 and MIBI defect size in patients studied at rest and in whom a myocardial infarction was responsible for a locally irreversibly impaired blood flow. Under these conditions of stabilized myocardial disease, it can be hypothesized that the tracer distribution in the myocardium was similar with both tracers. A former study[18] reports there was significantly reduced Tl-201 activity in the inferior wall when compared with MIBI activity, suggesting a potential role played by tissue depth attenuation. However, the present results demonstrate that this effect is not great enough to significantly modify the size of a defect. This is possibly due to the fact that a defect is represented by a more profoundly depressed uptake than the relative hypoactivity resulting from depth attenuation. Therefore, it seems that any difference that could appear between the defect size measured with Tl-201 and MIBI is not the consequence of the imaging conditions. Another possible explanation could be that the method of defect size calculation, which uses a fixed threshold, would work in infarcts because they represent dense defects, but not in exercise-induced defects, which usually contain some residual activity. However, even the visual examination of the views usually confirms the result of the calculation (Figure 6).

Therefore, the differences in defect size observed at exercise, redistribution and rest in patients with coronary artery disease is very likely due to differences in the tissular tracer distribution. According to the values obtained in the present study, the defect seen with MIBI is usually smaller than that seen with Tl-201. Other investigators have reported similar findings when comparing stress-rest MIBI and Tl-201 tomographic images in patients with coronary artery disease.[15] Their method of defect size calculation was based on a different approach from that used in this study, but they obtained similar results (the stress MIBI defects were smaller than the stress Tl-201 defects in 15 of 24 patients).

Whether these differences are clinically relevant in the routine diagnosis of coronary artery disease requires further clinical investigations.

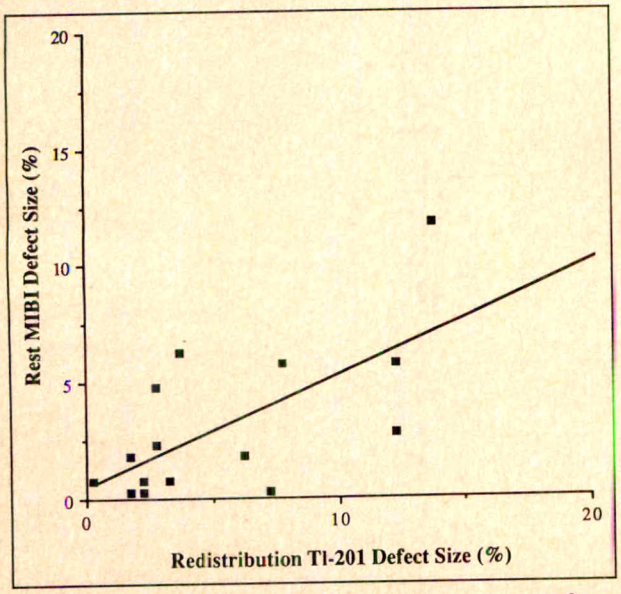


FIGURE 5. Comparison between the defect size measured on single-photon emission computed tomographic images with thallium-201 (Tl-201) at redistribution and methoxyisobutyl isonitrile (MIBI) at rest in 15 patients with proven coronary artery disease. Regression analysis yielded the following values: y = 0.34 + 0.48x, r = 0.65; SEE = 2.59%. Similar to images during exercise, mean defect size was smaller with Tl-201 than with MIBI, and the correlation was much weaker than when both agents were compared in patients who underwent imaging at rest.

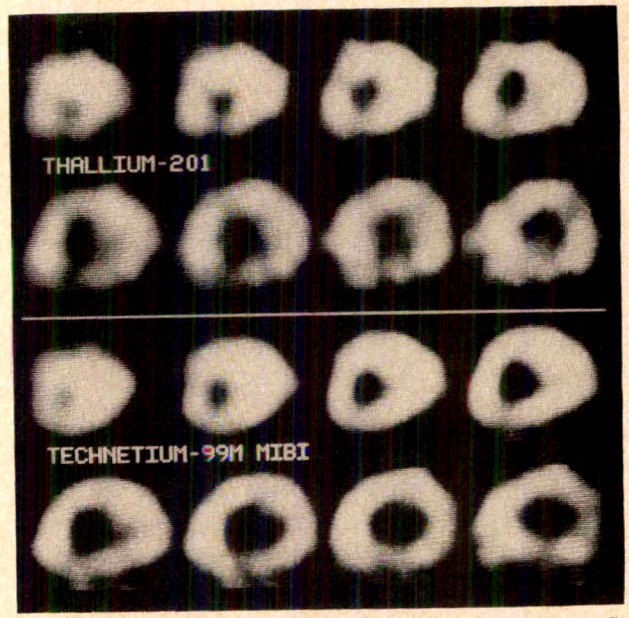


FIGURE 6. Series of adjacent sagittal sections (not reoriented) obtained in the same patient after injection at peak exercise with thallium-201 *(upper views)* and methoxyisobutyl isonitrile (MIBI) *(lower views)*. The 2 studies were performed on 2 different days. The apicoinferior defect is much better seen with thallium-201. Technically, both series of 8 views were scaled to their own maximum and the same relative cutoff level was used for gray-scale presentation.

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Effectiveness of Decremental Diameter Balloon Catheters (Tapered Balloon)

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Natural tapering of coronary arteries from larger proximal to smaller distal diameters often creates a dilemma for optimal balloon sizing during percutaneous transluminal coronary angioplasty (PTCA). To demonstrate the need for new dilating catheters suitable for tapered coronary anatomy, 100 consecutive coronary arteries were measured by videodensitometry, 1 cm proximal and distal to the stenosis. In 23 arteries there was a 1 mm or greater taper and 19 arteries showed a 0.5 to 0.99 mm taper. Only 50 arteries showed a nearly uniform diameter at the site of the stenosis, and 8 arteries demonstrated reverse taper, i.e., distal was greater than proximal diameter. To avoid balloon size mismatch with significant tapering, decremental diameter balloon catheters were developed. Series I tapers from 3.5 to 3.0 mm and series II from 3.0 to 2.5 mm over a balloon length of 25 mm. Tapered balloons were used in 80 patients with 94 tapered coronary arteries. Before PTCA, proximal, stenotic and distal mean diameters measured 3.6, 1.1 and 2.6 mm, respectively; after PTCA, proximal, stenotic and distal diameters measured 3.6, 2.8 and 2.5 mm, respectively, thus maintaining the natural tapering after effective dilatation. Only 2 arteries (2.1%) showed significant dissection, with no abrupt occlusions, and none requiring bypass surgery. In summary, decremental diameter balloon catheters provide optimal dilation in tapered arterial segments with few complications and offer a new approach to balloon sizing.

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Percutaneous transluminal coronary angioplasty (PTCA) has become an established method for myocardial revascularization.[1–7] Adequate dilation, i.e., dilating with a balloon large enough to avoid a large residual stenosis and a high risk of restenosis,[8,9] or a balloon small enough[10] to decrease the risk of coronary dissection or abrupt occlusion, is paramount for obtaining good results. Optimal balloon sizing is extremely difficult in tapered coronary arteries when the proximal arterial diameter is larger than the distal segment past the area of stenosis. To date, no consideration has been given to the tapering diameter of the coronary artery segment being dilated. Conventional balloons of uniform diameter risk dissection and abrupt closure of the narrower distal segment of the vessel. In addition, the decreasing vessel diameter places more demand on the accurate placement of the catheter and the need for selection of an optimally sized balloon. Decremental diameter balloon catheters were developed, as custom devices, for dilation of stenoses in such segments.[11] This report documents the incidence and severity of tapering found in coronary arteries and summarizes our subsequent experience with 2 series of decremental diameter balloon catheters — a new design in which the distal diameter is 0.5 mm smaller than the proximal diameter of the balloon.

METHODS

Video densitometric analysis of coronary segments: To document the incidence of tapering coronary anatomy, retrospective analysis of the cineangiograms of 100 consecutive patients who underwent PTCA at the Episcopal Heart Institute in 1988 was performed. Using a Vanguard model XR-70 coronary analyzer, measurements of the diameter and cross-sectional area of the segment were performed 1 cm proximal to the stenosis, at the stenosis, and 1 cm distal to the stenosis. From these measurements, mean diameters of the proximal, stenotic and distal segments were calculated and the number of vessels having <0.5 mm, 0.5 to 0.99 mm and ≥ 1.0 mm of taper were extracted.

The results of our evaluation documented the need for a new catheter design better suited to tapering coronary anatomy. Two generations of decremental diameter balloon catheters were custom-designed in collaboration with the U.S.C.I. Bard Corporation. The first generation used polyvinyl chloride balloon material in the U.S.C.I. LPS-I design. The second generation used polyethylene terephthalate balloon material in the U.S.C.I. sprint design. In each catheter design, 2 balloon sizes were available. The larger size had a proximal diameter of 3.5 mm and a distal diameter of 3.0 mm.

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TABLE I Frequency of Arterial Tapering Distal to Stenosis

	Taper	No. of Vessels	Proximal Mean Diam. (mm)	Distal Mean Diam. (mm)	p Value
Group A	<0.5 mm	50 (50%)	3.24 ± 1.21	3.23 ± 1.23	
Group B	0.5 to 0.99 mm	19 (19%)	3.42 ± 0.91	2.74 ± 0.95	<0.001
Group C	≥1 mm	23 (23%)	4.28 ± 1.28	2.8 ± 1.17	<0.001
Group D	Reverse taper	8 (8%)	4.07 ± 1.76	5.15 ± 1.82	

Diam. = diameter.

The smaller size had a proximal diameter of 3.0 mm and a distal diameter of 2.5 mm. All balloons had a length of 25 mm. Figure 1 shows the design of the decremental diameter balloons.

Patient selection: Patients undergoing PTCA with the decremental diameter balloons were selected only on the basis of tapering coronary anatomy; otherwise they were not selected. When a vessel showed tapering beyond the stenosis by visual estimation, an appropriately sized decremental diameter balloon was selected. Video densitometry was not used to select patients for PTCA with these balloons. Each patient gave informed consent.

Operative technique and medications: Dilating systems all used the conventional percutaneous femoral approach with conventional preformed guiding catheters, over-the-wire dilating catheters, and 0.014-inch guidewires. All lesions requiring large balloons (3.5 to 3.0 mm) were predilated with conventional but intentionally undersized cylindrical balloons of 2.0 or 2.5 mm diameter as per the routine of our laboratory. This had the added benefit of restoring enough blood flow to adequately visualize the best distal diameter. Dilating catheters were then exchanged for decremental diameter balloon catheters over extended guidewires, maintaining the wire distal to the lesion. For vessels requiring small balloons (3.0 to 2.5 mm), only a tapered balloon was used and predilation was not performed. Large decremental diameter balloons (3.5 to 3.0 mm) were used in 56% of lesions and small (3.0 to 2.5 mm) decremental diameter balloons were used in 44% of lesions.

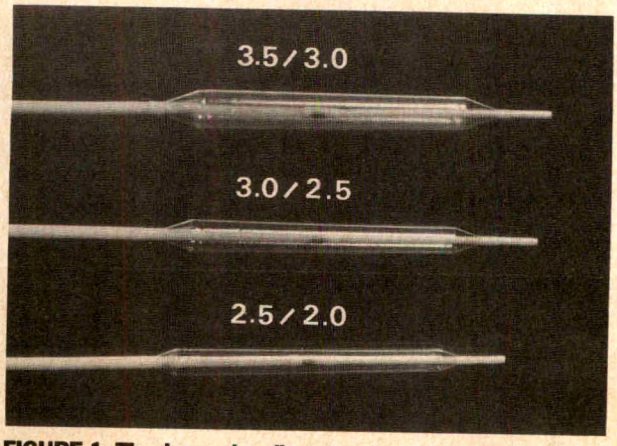


FIGURE 1. The decreasing diameter of the balloon is seen from the proximal to the distal end. Balloon length is 25 mm. The 3 sizes under investigation are: *top*, 3.5 mm tapered to 3.0 mm; *middle*, 3.0 mm tapered to 2.5 mm; and *bottom*, 2.5 mm tapered to 2.0 mm.

Conventional premedication with calcium antagonists and aspirin was given to all patients. Conventional post-PTCA care included 8 to 24 hours of intravenous heparin.

RESULTS

Frequency of coronary artery tapering: The tapering in 100 coronary stenotic segments is summarized in Figure 2, illustrating a symmetrical frequency distribution. It is evident from this graph that there is a significant variability from the mean with regard to the taper of the artery distal or proximal to the stenosis. Whereas most of the arteries analyzed have >0.4 mm of taper distal to the stenosis, a small number indicate that a proximal taper may also exist.

Clinically useful subgroups of coronary artery tapering include: group A, <0.5 mm taper (uniform or nearly uniform); group B, 0.5 to 0.99 mm taper (significant tapering); group C, ≥1.0 mm taper (marked tapering); and group D, reverse taper (distal diameter greater than the proximal diameter).

Table I shows the distribution of arteries in the 4 subgroups. It is apparent that only 50% of the arteries maintain a uniform or nearly uniform diameter proximal and distal to the stenosis. Nineteen percent showed a significant taper and 23% showed marked tapering distal to the stenosis. Thus, fully 42% of the coronary arteries would require a decremental diameter balloon to optimally match the size of the balloon to the size of the artery. In 8% of the arteries, the diameter of the artery proximal to the stenosis was smaller than the diameter distal to the stenosis.

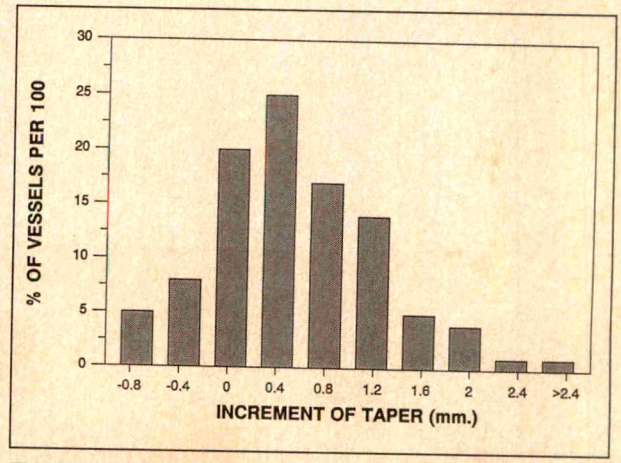


FIGURE 2. The frequency distribution curve for tapering of coronary arteries in 100 coronary stenotic segments undergoing percutaneous transluminal coronary angioplasty.

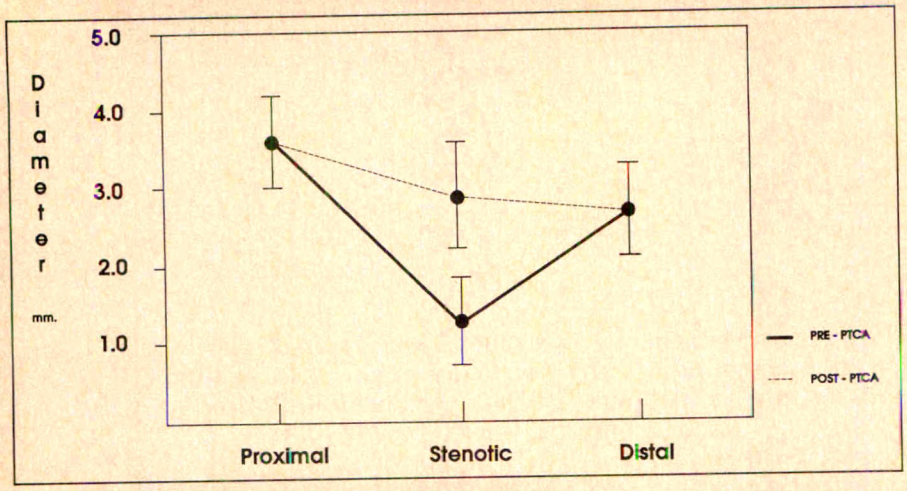


FIGURE 3. Quantitative angiographic measurement of diameter of the coronary arteries as determined by videodensitometry before (PRE) and after (POST) percutaneous transluminal coronary angioplasty (PTCA) (see text).

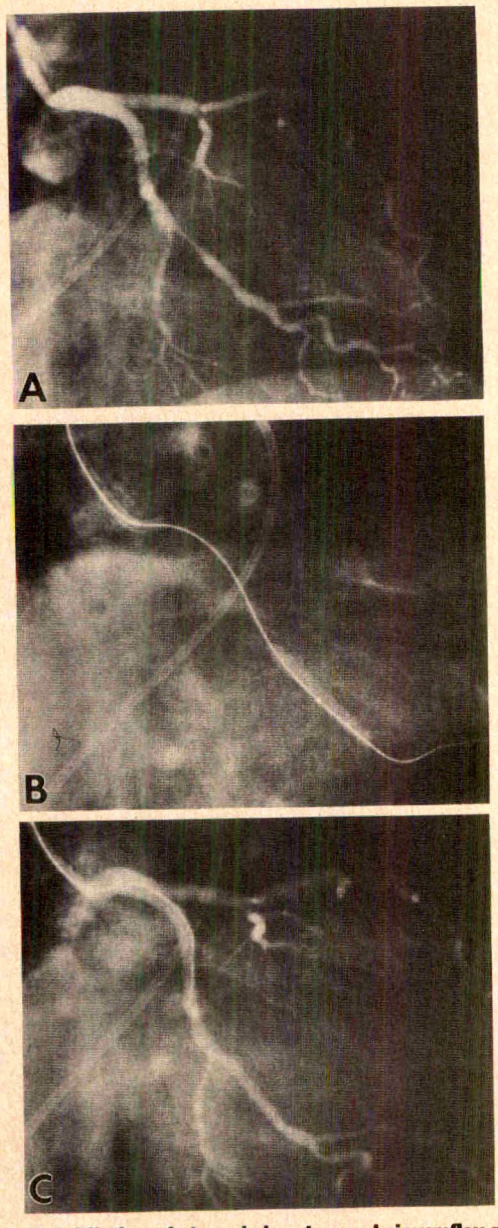


FIGURE 4. Dilation of stenosis in a tapered circumflex marginal artery (right anterior oblique view). *A*, significant tapering of the artery distal to stenosis; *B*, tapered 3.5 to 3.0 mm balloon in position; *C*, excellent result after percutaneous transluminal coronary angioplasty.

Outcome of dilation with decremental diameter balloon: Angioplasty was performed in 80 patients with 102 stenoses in 94 tapered coronary arteries, for an overall success rate of 98%. The most frequent vessel requiring a decremental diameter balloon was the left anterior descending artery (n = 66) although other arteries (i.e., circumflex [n = 11], right coronary [n = 10], branch vessels [n = 10] and bypass grafts [n = 5]) frequently showed significant tapering as well. Of the 102 tapered coronary segments, 10 had total occlusion in which the diameter of the artery distal to the occlusion was unknown, and predilation with a 2.0 mm conventional balloon and establishment of flow allowed determination of a distal tapered diameter. An appropriately sized, decremental diameter balloon was then advanced over the extended wire and maximal dilatation achieved. There were only 2 unsuccessful dilations, 1 related to heavy calcification in the left anterior descending artery and another related to failure to cross in an extremely angulated right coronary artery. Of the 10 patients with total occlusions all were successfully dilated with these balloons.

Figure 3 shows the typical quantitative angiographic results of dilation with the decremental diameter balloon catheter. With use of videodensitometry, the vessel diameters were measured and averaged. Before dilation, the proximal diameter measured 3.6 ± 0.6 mm, the stenotic diameter measured 1.1 ± 0.5 mm, and the distal diameter measured 2.6 ± 0.7 mm. After dilation with this balloon, the proximal diameter measured 3.6 ± 0.7 mm, the dilated segment diameter measured 2.8 ± 0.7 mm and the distal segment measured 2.5 ± 0.6 mm, thus demonstrating both excellent dilation of the stenosis (average area of stenosis 86 to 14%), as well as restoration of the natural taper of the artery.

Figure 4 illustrates a typical tapered segment with a stenosis in a circumflex marginal artery, the balloon in position, and the PTCA result. Figure 5 shows an example of a totally occluded artery in which the size and configuration of the distal vessel is not known until the vessel is predilated. After the initial dilation with a conventional 2.0 mm balloon, a tapered vessel was discovered. The final result of dilation with this balloon is shown. Figure 6 demonstrates a mismatch between the size of the vein graft and native left anterior descending

artery. The stenosis at the anastomosis was dilated with a tapered balloon with an excellent result.

Since the final preparation of this report, a smaller size decremental diameter balloon tapering from 2.5 to 2.0 mm has also been developed and has been successfully utilized in distal vessels, providing optimal PTCA results in 6 patients with very distal left anterior descending and circumflex marginal stenoses.

The technique of predilation with an undersized balloon and dilation with a tapered balloon for larger vessels and the use of matched tapered balloons for smaller vessels resulted in minimal complications. There were 2 instances of dissection (2.1%). In 1 patient, dissection was noted after the initial dilation with the conventional 2.5 mm balloon and was extended when the lesion was further dilated with a 3.5 to 3.0 mm decremental diameter balloon. In the other case, dissection appeared only after dilation with the 3.5 to 3.0 mm balloon. Retrospective analysis did not suggest significant mismatch in the balloon and vessel size. In both cases there was excellent flow distal to the dissection and neither patient required coronary artery bypass surgery. There were no

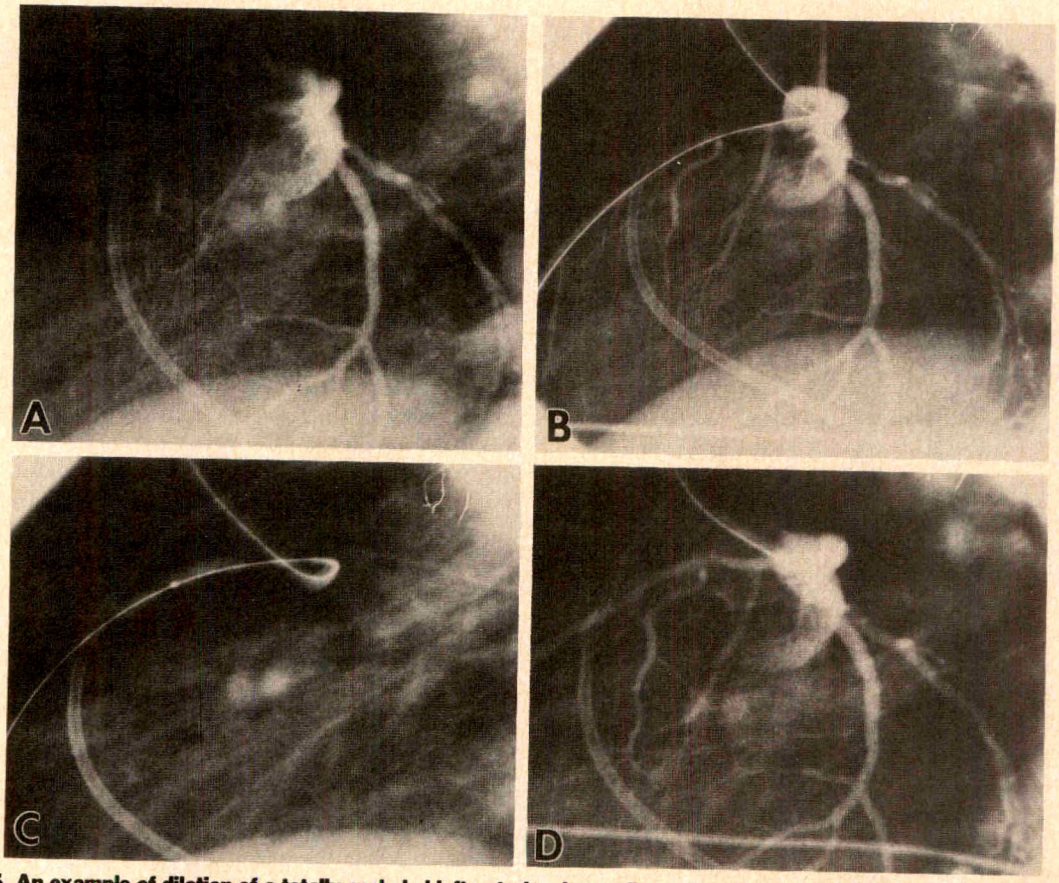


FIGURE 5. An example of dilation of a totally occluded left anterior descending artery (left lateral view). *A*, total occlusion of proximal left anterior descending artery with faint or no visualization of distal vessel; *B*, visualization of tapered distal vessel after predilation with a conventional 2 mm balloon; *C*, tapered 3.5 to 3.0 mm balloon in position; and *D*, excellent result after percutaneous transluminal coronary angioplasty.

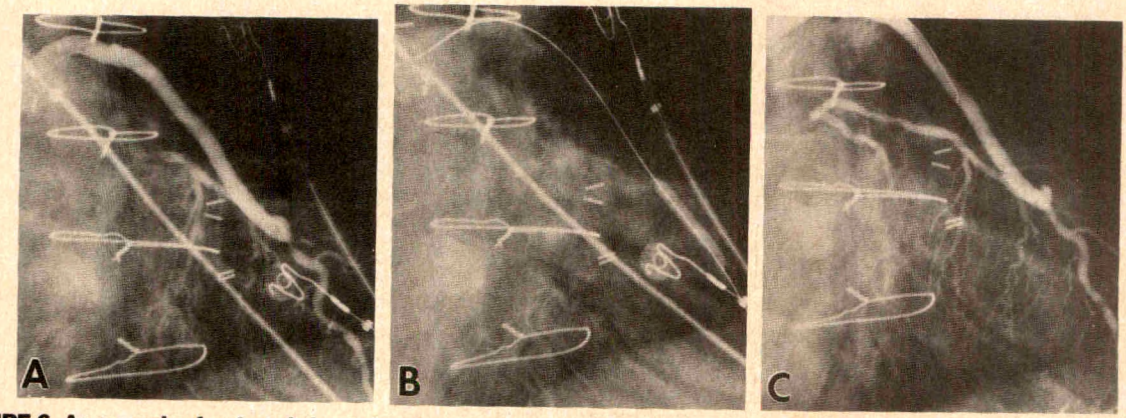


FIGURE 6. An example of a stenosis located at the anastomotic site of a left anterior descending artery graft showing marked mismatch in the size of the graft and distal left anterior descending artery (right anterior oblique view). *A*, stenosis at the anastomotic site; *B*, 3.0 to 2.5 mm balloon in position; and *C*, excellent result after percutaneous transluminal coronary angioplasty.

instances of abrupt closure, no emergency coronary bypass surgery, no in-hospital myocardial infarction and no death in this selected group of patients.

DISCUSSION

The safety and efficacy of PTCA are directly related to the match in size between the dilating balloon and the arterial segment. Conventional balloon catheters have uniform diameters along the length of the balloon and are not ideally fitted for tapered arteries. In the larger proximal segment, the balloon is relatively undersized and provides inadequate dilation. In the smaller distal segment, the balloon is relatively oversized and provides excessive dilation increasing intimal and medial injury and risking dissection and abrupt closure. An optimally sized tapered balloon with decremental diameters over the length of the balloon can potentially provide a more optimal dilation in such tapered arterial segments without risking excessive injury to the narrower distal segment. This may avoid severe dissection and abrupt closure.

This study reveals that only 50% of coronary artery segments subjected to PTCA have uniform or nearly uniform diameters (<0.5 mm of taper). Nineteen percent showed significant (0.5 to 0.99 mm) tapering and 23% showed marked (≥1.0 mm) tapering. Fully 42% of the vessels studied had a nonuniform diameter. For these coronary segments, none of the available conventional balloons could provide an ideal match for the size of the artery. Without decremental diameter balloons, these segments could be underdilated accepting greater residual stenosis or overdilated, risking dissection and closure. Another 8% of the segments showed reverse tapering in which the distal diameter was greater than the proximal diameter. These segments would also be underdilated with the currently available conventional balloon systems.

Since conventional balloon angioplasty is not always able to provide an optimal final appearance, other techniques (i.e., atherectomy, stenting or laser-assisted balloon angioplasty) have been increasingly popular. Most of these techniques are limited to the proximal segments of vessels which do not have an angulated approach and none has been able to reduce the rate of restenosis.[12–14] Simple balloon angioplasty continues to be the most important technique of choice for revascularization of distal segments or multiple sites, as well as in more tortuous coronary anatomy. To improve the final angiographic appearance and reduce the risks of PTCA, a more optimal match of balloon to artery has to be achieved.

The decremental diameter (tapered) balloon catheter provides excellent dilation of the stenosis while maintaining the natural taper of the artery. Figures 4 to 6 are clear illustrations of segments in which conventional cylindrical balloons could not have achieved an appropriate fit. An optimal fit of the balloon to the dilated segment will provide a more ideal dilation, while minimizing injury to the smaller distal segment. The incidence of complications in these patients was extremely small. Only 2 of the 102 (2.1%) stenotic segments showed dissections and none required further intervention. There was no in-hospital complication, no abrupt occlusion, no emergent coronary bypass, no myocardial infarct and no mortality. Ongoing experience with decremental diameter balloons indicates that these dilating catheters provide excellent dilation at tapered coronary segments without significant risk of dissection. As an expected advantage, they also provide an easier approach to balloon sizing during PTCA. The position of the wedge profile of the balloon provides a continuous range of inflated diameters at the stenosis. Slightly advancing or withdrawing the tapered balloon changes the diameter fractionally at the stenosis without the need for excessive pressure or compliant balloons for achieving optimal PTCA results. In 2 patients, 3-vessel coronary angioplasty with multiple stenoses was performed with a single decremental diameter balloon (3.0 to 2.5 mm) which provided optimal results in all lesions because of the continuous range of diameters available for optimal sizing.

The decremental diameter balloon catheter offers a new and potentially safer approach to optimal balloon sizing in selected vessels. Catheters of newer, lower profile construction will allow improved distal passage of these balloons in tortuous arteries. Further development of different sizes of tapered balloons is in progress.

These balloons may also be combined with newer adjuncts to balloon angioplasty such as atherectomy, laser angioplasty and stents. Optimal stenting in tapered coronary segments may require tapered balloon carriers to achieve optimal results and avoid unnecessary stresses at the edge of the stent in the narrower distal segment. Directional atherectomy devices could restore the normal appearance of tapered arteries with reduced risks of severe injury to the distal media if the positioning balloon were appropriately tapered. Optimal fit of balloon to vessel may more fully optimize the result of laser balloon angioplasty.

The long-term effect of matching the balloon diameter and improving balloon fit in tapered coronary segments has not been determined. It is conceivable that minimizing injury to the intima and media of the narrower distal arterial segment may favorably affect the restenosis rate. Further studies on restenosis rates in tapered coronary segments are warranted. A larger, multicenter experience with decremental diameter balloons is necessary to confirm the efficacy, safety and long-term effects.

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Postangioplasty Restenosis Rate Between Segments of the Major Coronary Arteries

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Conflicting data have been published regarding the rate of postangioplasty restenosis observed in diverse segments of the coronary tree. However, these studies may be criticized for their biased selection of patients, methods of analysis, and definitions of restenosis. In the present study, 1,353 patients underwent a successful coronary dilatation of ≥1 site. In all, 1,234 patients (91%) had a follow-up angiogram after 6 months, or earlier when indicated by symptoms. All films were processed and analyzed at the thoraxcenter core laboratory with the coronary angiography analysis system (automated contour detection). Restenosis was considered present if the diameter stenosis at follow-up was >50%. No differences in restenosis rates were observed between coronary segments using this categorical definition. A continuous approach was also used; absolute changes in minimal luminal diameter adjusted for vessel size were used in order to allow comparison between vessels of different sizes (relative loss). No significant differences were observed between the coronary segments with this continuous approach. These results suggest that restenosis is a ubiquitous phenomenon without any predilection for a particular site in the coronary tree.

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Ever since the introduction of percutaneous transluminal coronary angioplasty (PTCA)[1] as an alternative to coronary artery bypass grafting, this means of treatment has been plagued by the problem of restenosis, which has become an important field of investigation in interventional cardiology. During the last 14 years clinicians have searched extensively for factors increasing the risk of restenosis, and many patient-lesion-procedure–related factors have been put forward.[2,3] However, the cause and effect relation of these factors can be questioned, because these early studies were, in general, retrospective analyses with relatively small numbers of patients. In addition, these studies were fraught with methodologic problems; angiographic follow-up was incomplete, incidence of restenosis was influenced by the recurrence of symptoms, and time for restudy was not predetermined. Furthermore, the definition of restenosis varied between the different studies, and presence or absence of restenosis was assessed visually, a method known to be limited by inter- and intraobserver variability.[4,5] One risk factor for restenosis that led to controversy is the site of dilatation, with some studies finding a higher incidence of restenosis in the proximal left anterior descending coronary artery (LAD) as compared with the right or left circumflex coronary artery (LC) (Table I).[6–19] Recently, 2 multicenter restenosis prevention trials enrolled >1,400 patients who were analyzed at the same angiographic core laboratory. In 91% of these patients, follow-up angiography was performed, and the same quantitative coronary angiographic method of analysis was used.[5,20] The present study investigates whether the previously reported differences in restenosis rates in the 3 major coronary arteries could be confirmed in this large study group.

METHODS

The study population consisted of 1,442 patients with significant primary stenoses in native coronary arteries who were prospectively enrolled in 2 restenosis trials in Europe. Because no angiographic or clinical benefit of the 2 tested compounds could be demonstrated, the control and active treatment groups were pooled for the present study. PTCAs and follow-up films of all patients with successful dilations were analyzed at the thoraxcenter core laboratory. Informed consent was obtained in all cases before the PTCA procedure, and all patients were asked to return to the hospital for follow-up angiography. Patients with stable and unstable angina pectoris, and those with totally occluded vessel segments were included in the study. Pa-

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TABLE I Summary of Restenosis Studies Demonstrating Conflicting Results as to the Site of Dilatation as a Risk Factor for Restenosis

Study	Year	Patients	Angio Fup (%)	Definition of Restenosis	Restenosis (%)	Coronary Artery	Statistical Analysis
Holmes[6]	1984	665	84	NHLBI I→IV	33.6	No difference	Multivariate
Kaltenbach[7]*	1985	356	94	DS Fup <20% DS pre	12	No difference	Univariate
				Decrease ≥50% of gain	16		
				↑ DS ≥30%	17		
Mata[8]†	1985	63	95	↑ DS >30% or DS >70%	23	LAD or LC >right	Multivariate
DiSciascio[9]†	1986	191	21¶	Decrease ≥50% of gain	58 1-VD 42 2-VD	No difference	Univariate
Leimgruber[10]	1986	1,758	57	>50% DS	30.2	LAD >right >LC	Multivariate
Myler[11]‡	1987	286	57	>50% DS	41	No difference	Multivariate
Val[12]	1987	181	98	↑ ≥30% DS	28	No difference	Multivariate
Vandormael[13]‡	1987	209	62	>50% DS	82 (Symp) 30 (No Symp)	LAD >right or LC Prox >Dist	Multivariate
Black[14]§	1988	384	39	>50% DS	31	No difference	Multivariate
de Feyter[15]‖	1988	179	88	>50% DS	32	LAD >right or LC	Multivariate
Fleck[16]*	1988	110	86	ΔMLCA >1 mm² (QCA)	58	No difference	Multivariate
Quigley[17]§	1989	114	88	>50% DS	32	No difference	Multivariate
Renkin[18]	1990	278	47**	>50% DS	—	No difference	Multivariate
Rupprecht[19]*	1990	676	70	>50% DS or decrease >50% of gain	29.2	No difference	Multivariate
Present study	1991	1,353	91	>50% DS	31	No difference	Univariate
				Relative loss	0.11 ± 0.21		Analysis of variance

*Excluded total occlusions; †multivessel dilatation; ‡multilesion dilatation; §for restenosis; ‖unstable angina; ¶review of patients with clinical recurrence; **angiography + exercise thallium scintigraphy.

Angio Fup = % of patients with angiographic follow-up; Dist = distal; DS = diameter stenosis; LAD = left anterior descending; LC = left circumflex; ΔMLCA = change in minimal luminal cross-sectional area; NHLBI = National Heart, Lung, and Blood Institute; pre = before; Prox = proximal; QCA = quantitative coronary angiographic method of analysis; RCA = right coronary artery; Symp = symptoms; VD = vessel disease.

tients with developing myocardial infarctions and significant left main disease were excluded from the study. PTCA was successful if the final diameter stenosis was <50% on visual inspection of the angiogram after PTCA. PTCA was considered complete when the guiding catheter was removed from the groin. When recurrence of chest pain during the hospital stay led to coronary reintervention, the film before reintervention was used as the follow-up angiogram. If a follow-up angiogram was obtained before 3 months and if no definite restenosis had occurred, the patient was asked to undergo another coronary angiogram at 6 months.

Figure 1 describes the flow chart of all 1,442 randomized patients. Of the 1,353 patients with successful PTCA, 1,234 patients had a follow-up angiogram after 6 months, or earlier when indicated for symptoms.

Percutaneous transluminal coronary angioplasty procedure and angiographic analysis: At the beginning of the procedure, all patients received a bolus of intravenous heparin (10,000 IU). After 2 hours, an additional infusion of heparin (5,000 IU/hour) was administered until the end of the procedure. Use of a calcium antagonist for 48 hours was permitted. Choice of balloon type, inflation duration and pressure was left to the discretion of the operator.

Three angiograms were obtained of each patient (1 immediately before and 1 immediately after PTCA, and 1 at follow-up). The angiograms were recorded in such a way that they were suitable for quantitative analysis by the coronary angiography analysis system. An example of an analysis is shown in Figure 2. To standardize the method of data acquisition and to ensure exact reproducibility of angiograms after PTCA and at follow-up, measures were taken as described previously.[5,20]

All cineangiograms were quantitatively analyzed using the coronary angiography analysis system that has been validated and described in detail previously.[5,20] The absolute values of the stenosis diameter as well as the reference diameter are measured by computer using the known contrast-empty catheter diameter as a scal-

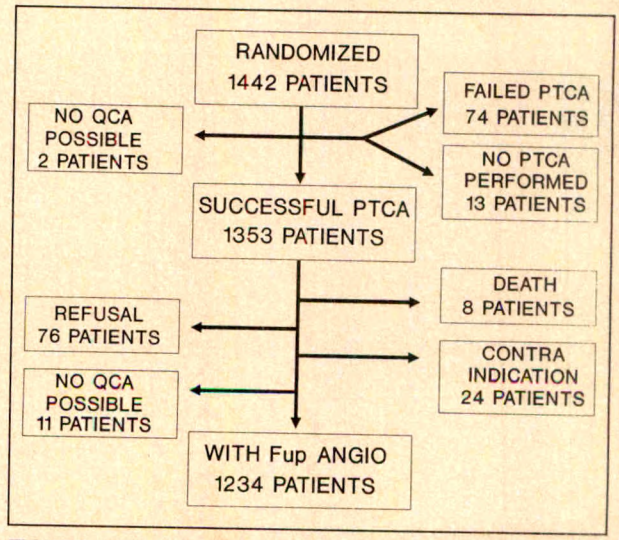


FIGURE 1. Flow chart of 1,442 randomized patients. In 74 patients, angioplasty procedure was unsuccessful, in 13, percutaneous transluminal coronary angioplasty (PTCA) was not performed, and in 2, quantitative analysis (QCA) was not possible. Angiographic follow-up (Fup ANGIO) was obtained in 1,234 patients (91%) after successful coronary angioplasty in 1,353.

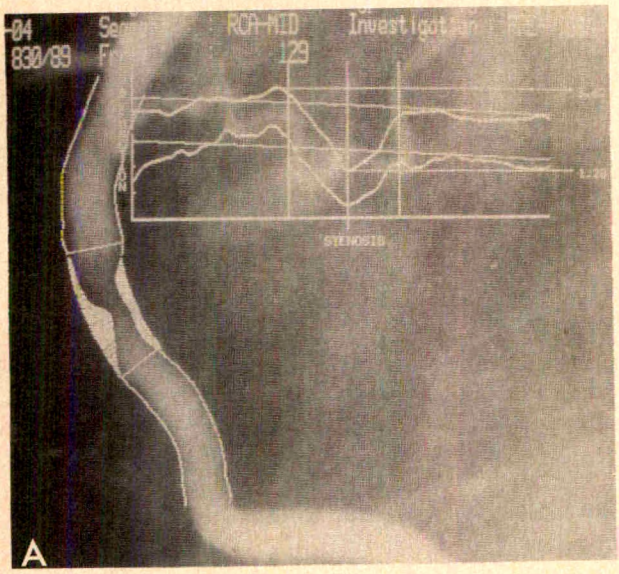
ing device. For that purpose, the catheter tips were retained for accurate measurement with a micrometer. To achieve maximal vasodilation, either nitroglycerin (0.1 to 0.3 mg) or isosorbide dinitrate (1 to 3 mg) was administered for each coronary artery involved before and after PTCA, and at follow-up angiography. All contour positions of the catheter and the arterial segment were corrected for pincushion distortion introduced by the image intensifiers. Because the algorithm is not able to measure total occlusions and lesions with Thrombolysis in Myocardial Infarction-1 perfusion, a value of 0 mm was substituted for the minimal luminal diameter and 100% for the percent diameter stenosis. In these cases, the reference diameter after PTCA was substituted for the reference diameter before PTCA or at follow-up. For each dilated segment, the minimal luminal diameter and diameter stenosis before and after PTCA, and at follow-up were taken as the mean value from multiple matched projections.[5]

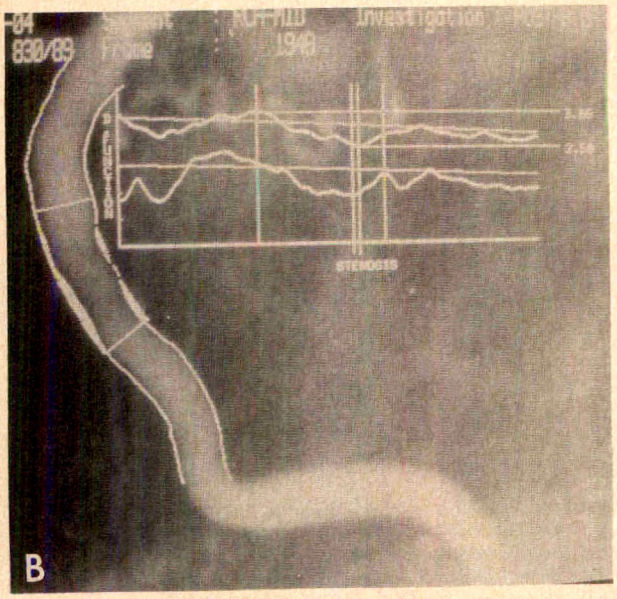
Definition of coronary segments: Austen et al[21] divided the coronary tree in 15 different segments (Figure 3). Because dilatation of the distal vessel segments did not occur frequently, it was decided to regroup these distal segments. The right coronary artery was divided in 4 segments; segment 1 corresponded with the proximal, segment 2 with the middle, and segments 3 and 4 were taken together as the distal right coronary artery. The LAD was divided in 5 segments; segment 6 corresponded with the proximal LAD, segment 7 with the middle LAD, and segments 8, 9 and 10 were taken together as the distal LAD. The LC was divided in 5 segments; segment 11 corresponded with the proximal LC, segments 13 and 15 were taken together as the middle LC, and segments 12 and 14 were taken together as the distal LC.

Definition of restenosis: CATEGORICAL APPROACH: Many criteria have been proposed by the National Heart, Lung, and Blood Institute to assess restenosis. The most frequently used criterion by clinicians is that restenosis is present when the diameter stenosis is >50% at follow-up angiography.[22] This definition was used for our data.

CONTINUOUS APPROACH: In addition to this arbitrary categorical approach for restenosis, we wanted to use absolute changes in minimal luminal diameter adjusted for vessel size, which allows for comparison between vessels of different sizes and is a reflection of how the lesion behaves during and after PTCA.

Relative gain depicts the increase in minimal luminal diameter normalized for the reference diameter during PTCA (minimal luminal diameter [before PTCA − after PTCA]/reference diameter before PTCA). Relative loss depicts the decrease in minimal luminal diameter normalized for the reference diameter (minimal lu-





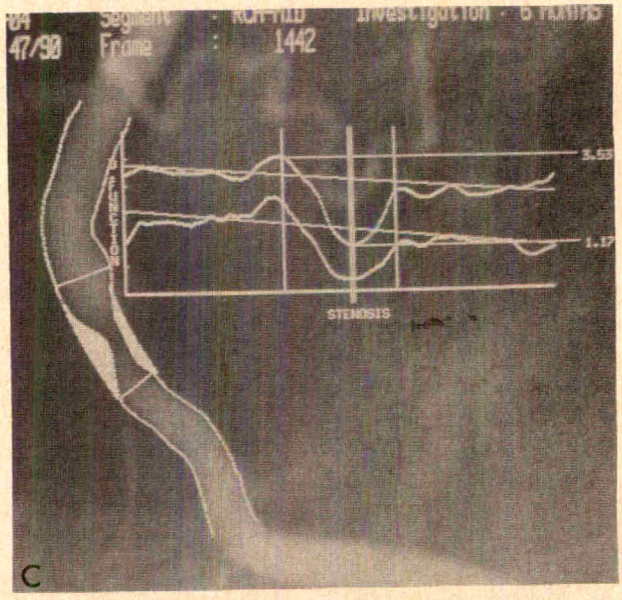


FIGURE 2. Single frame angiograms of same lesion of the right coronary artery before dilatation *(A)*, after dilatation *(B)* and at follow-up *(C)*. Arterial boundaries detected by system are shown on angiogram; *upper curve* represents diameter function curve. Minimal luminal diameter changes from 1.28 before to 2.58 mm after percutaneous transluminal coronary angioplasty. At follow-up 6 months later there is a decrease of minimal luminal diameter to 1.17 mm.

minal diameter [after PTCA – at follow-up]/reference diameter before PTCA) (Figure 4).

Data analysis: Data were analyzed using the biomedical-designed program statistical software package (University of California Press, Berkeley, California, 1990). A chi-square test was used to assess differences in categorical variables. A 1-way analysis of variance was used to assess differences in continuous variables among the 3 major coronary arteries and the 9 different segments of the coronary tree. A p value <0.05 was considered indicative of a significant difference.

RESULTS

The mean time to follow-up angiography was 165 ± 42 days. In 1,234 patients, 1,452 lesions were successfully dilated (1.2 lesions/patient). In 74 patients, a totally occluded vessel segment was dilated. In 1,137 patients, 1-vessel dilatation was performed, 93 had 2-vessel dilatation, and 4 had all 3 vessels dilated. The majority of stenoses were located in the LAD (684 lesions) compared with 414 lesions in the right coronary artery and 354 in the LC.

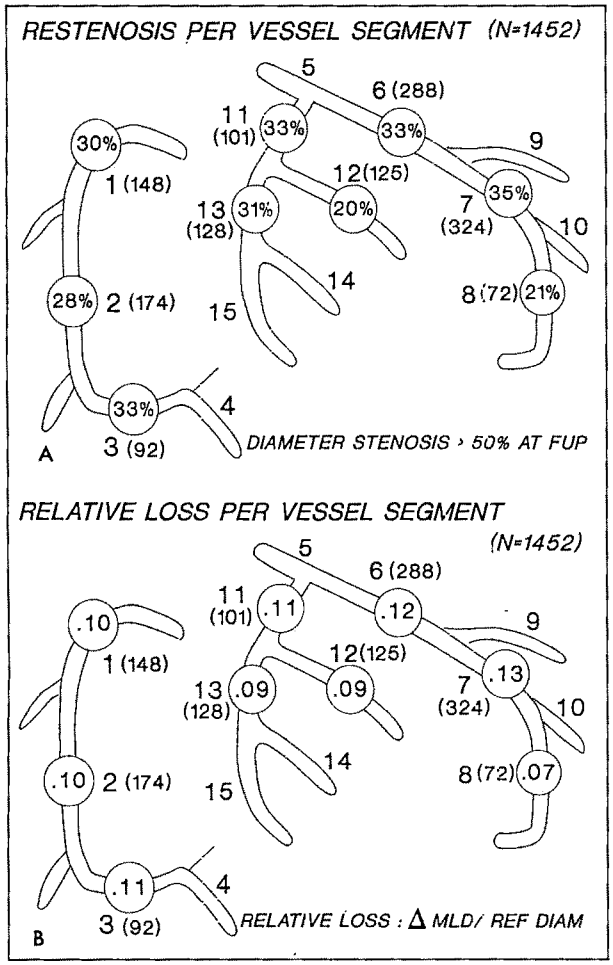


FIGURE 3. Coronary tree divided in 15 different segments with restenosis rate (using >50% diameter stenosis as criterion) for each segment *(A)*, and relative loss per coronary segment *(B)* shown in *circles*. Between *brackets* are numbers of lesions dilated for that segment. FUP = follow-up. ΔMLD/REF DIAM = decrease in minimal luminal diameter normalized for reference diameter.

Table II lists the results of the quantitative measurements of the 1,452 lesions. The largest vessel was the right coronary artery, with an average reference diameter of 2.86 ± 0.55 mm. The LAD and LC had similar sizes; the average reference diameters were 2.54 ± 0.53 mm for the LAD, and 2.55 ± 0.50 mm for the LC ($p < 0.001$). In addition, the average increases in minimal luminal diameter were 0.82 ± 0.37 mm in the right coronary artery, 0.71 ± 0.36 mm in the LAD, and 0.72 ± 0.35 mm in the LC. If these values were "normalized for the reference diameter" (relative gain), no significant differences were observed among either the 3 major coronary arteries (right coronary artery vs LAD vs LC; $p = 0.44$) or the different segments of the coronary tree ($p = 0.77$). During follow-up, the average losses in minimal luminal diameter were 0.26 ± 0.55 mm in the right coronary artery, 0.30 ± 0.48 mm in the LAD, and 0.25 ± 0.48 mm in the LC. If these values were normalized for the reference diameter (relative loss), no significant differences were observed among the 3 major coronary arteries (right coronary artery vs LAD vs LC; $p = 0.13$) or the different segments of the coronary tree ($p = 0.19$).

The restenosis rate, and relative gain and loss for the 3 major coronary arteries and the diverse vessel segments, using either the categorical or continuous approach, are listed in Table III. No significant difference in either approach was observed.

DISCUSSION

Several investigators have raised the question as to whether the dilated vessel constitutes a risk factor for the development of restenosis. They have reported conflicting results (Table I). The question is becoming even more relevant as new interventional techniques (such as stenting, atherectomy, laser photoablation and rotablation) have been "claimed" to be more effective than conventional balloon angioplasty in certain lesion types (long lesions and total occlusions), locations or vessels (right coronary artery, LAD, LC and bypass graft),[23]

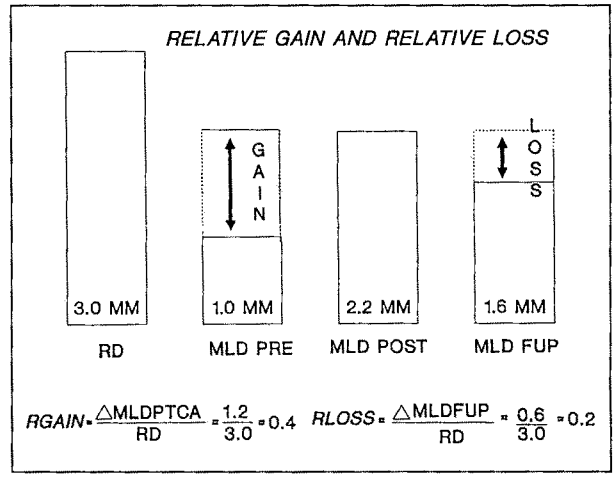


FIGURE 4. See text for explanation of relative gain (RGAIN) and relative loss (RLOSS). FUP = follow-up; MLD = minimal luminal diameter; POST = after; PRE = before; PTCA = percutaneous transluminal coronary angioplasty; RD = reference diameter.

although these new techniques have not yet succeeded in reducing restenosis rates.[24,25] Several explanations have been put forward to explain the increased risk for restenosis in the (proximal) LAD. Mata et al[8] believed that a high rate of "continuous success" needs an optimal selection of the balloon/artery ratio and optimal balloon pressure application. They suggested that anatomic or procedural factors were responsible for restenosis. Leimgruber et al[10] had 3 possible explanations. First, because they believed that the proximal LAD is

TABLE II Baseline Quantitative Angiographic Data per Vessel Segment Dilated

Coronary Artery	No.	Pre PTCA RD (mm)	Post PTCA RD (mm)	Follow-Up RD (mm)	Pre PTCA MLD (mm)	Post PTCA MLD (mm)	Follow-Up MLD (mm)
Total	1,452	2.63 ± 0.54	2.70 ± 0.52	2.70 ± 0.56	1.02 ± 0.38	1.77 ± 0.36	1.50 ± 0.57
Right	414	2.86 ± 0.55	2.93 ± 0.52	2.97 ± 0.58	1.08 ± 0.41	1.91 ± 0.37	1.65 ± 0.65
Proximal	148	2.99 ± 0.55	3.05 ± 0.51	3.07 ± 0.55	1.11 ± 0.45	1.96 ± 0.39	1.69 ± 0.63
Middle	174	2.82 ± 0.50	2.90 ± 0.50	2.94 ± 0.59	1.08 ± 0.41	1.91 ± 0.34	1.66 ± 0.65
Distal	92	2.71 ± 0.59	2.81 ± 0.56	2.85 ± 0.57	1.02 ± 0.35	1.83 ± 0.40	1.57 ± 0.66
LAD	684	2.54 ± 0.53	2.59 ± 0.49	2.58 ± 0.53	1.01 ± 0.36	1.72 ± 0.35	1.42 ± 0.53
Proximal	288	2.73 ± 0.52	2.78 ± 0.48	2.76 ± 0.53	1.08 ± 0.35	1.83 ± 0.35	1.53 ± 0.55
Middle	324	2.48 ± 0.47	2.52 ± 0.43	2.52 ± 0.47	0.97 ± 0.36	1.68 ± 0.32	1.35 ± 0.51
Distal	72	2.08 ± 0.44	2.14 ± 0.44	2.13 ± 0.42	0.87 ± 0.35	1.43 ± 0.29	1.29 ± 0.37
LC	354	2.55 ± 0.50	2.62 ± 0.46	2.61 ± 0.48	1.01 ± 0.36	1.73 ± 0.34	1.48 ± 0.51
Proximal	101	2.73 ± 0.47	2.75 ± 0.43	2.74 ± 0.44	1.06 ± 0.42	1.82 ± 0.32	1.52 ± 0.50
Middle	125	2.55 ± 0.50	2.64 ± 0.45	2.61 ± 0.50	1.00 ± 0.34	1.75 ± 0.32	1.52 ± 0.53
Distal	128	2.41 ± 0.49	2.50 ± 0.46	2.52 ± 0.48	0.98 ± 0.34	1.63 ± 0.34	1.41 ± 0.49

Values are means ± standard deviation.
LAD = left anterior descending; LC = left circumflex; MLD = minimal luminal diameter; Post = after; Pre = before; PTCA = percutaneous transluminal coronary angioplasty; RD = reference diameter.

TABLE III Restenosis Rate per Segment Using the Categorical Definition of > 50% DS at Follow-Up, and the Continuous Approach with Relative Gain and Loss

		DS (%) at Follow-Up > 50%			
	No.	Yes	No	Relative Gain	Relative Loss
Total	1452	444 (31)	1008 (69)	0.29 ± 0.16	0.11 ± 0.21
Right	414	123 (30)	289 (70)	0.30 ± 0.15	0.10 ± 0.22
Proximal	148	45 (30)	103 (70)	0.29 ± 0.15	0.10 ± 0.21
Middle	174	48 (28)	126 (72)	0.30 ± 0.15	0.10 ± 0.22
Distal	92	30 (33)	62 (67)	0.31 ± 0.15	0.11 ± 0.26
LAD	684	224 (33)	457 (67)	0.29 ± 0.17	0.12 ± 0.20
Proximal	288	95 (33)	193 (67)	0.29 ± 0.17	0.12 ± 0.19
Middle	324	114 (35)	210 (65)	0.29 ± 0.17	0.13 ± 0.21
Distal	72	15 (21)	57 (79)	0.27 ± 0.19	0.07 ± 0.15
LC	354	97 (28)	255 (72)	0.29 ± 0.16	0.11 ± 0.21
Proximal	101	33 (33)	68 (67)	0.29 ± 0.16	0.11 ± 0.18
Middle	125	25 (20)	100 (80)	0.30 ± 0.15	0.09 ± 0.21
Distal	128	40 (31)	88 (69)	0.28 ± 0.17	0.09 ± 0.21
p Value	(right vs LAD vs LC)	0.22		0.44	0.13
	(9 segments)	0.06		0.77	0.19

Values are means ± standard deviation.
Abbreviations as in Table I.

TABLE IV Relative Gain and Loss per Reference Diameter Group

						DS (%) at Follow-Up > 50%		
RD (mm)	No.	Absolute Gain (mm)	Relative Gain	Absolute Loss (mm)	Relative Loss	Yes	No	BAR
> 4.0 mm	18	0.72 ± 0.55	0.17 ± 0.13	0.13 ± 0.46	0.03 ± 0.10	6 (33)	12 (67)	0.77
3.5 to 4.0 mm	81	0.87 ± 0.47	0.24 ± 0.13	0.10 ± 0.50	0.03 ± 0.13	23 (28)	58 (71)	0.89
3.0 to 3.5 mm	222	0.83 ± 0.42	0.26 ± 0.13	0.33 ± 0.54	0.10 ± 0.27	71 (32)	151 (68)	0.97
2.5 to 3.0 mm	507	0.76 ± 0.40	0.28 ± 0.15	0.28 ± 0.52	0.10 ± 0.29	153 (30)	354 (70)	1.07
2.0 to 2.5 mm	454	0.72 ± 0.40	0.32 ± 0.17	0.28 ± 0.51	0.12 ± 0.23	148 (33)	306 (67)	1.20
< 2.0 mm	170	0.61 ± 0.34	0.34 ± 0.20	0.27 ± 0.46	0.15 ± 0.26	44 (26)	126 (74)	1.39
Analysis of variance		< 0.001	< 0.001	< 0.02	< 0.001	NS		

Values are means ± standard deviation.
BAR = balloon-artery ratio (size of the balloon according to manufacturer divided by the reference diameter before percutaneous transluminal coronary angioplasty); DS = diameter stenosis; NS = not significant; RD = reference diameter.

most often the largest artery, the 3.0 mm diameter balloons most frequently used at that time could have been undersized for the LAD and oversized for the right coronary artery and LC. This resulted in increased diameter stenosis after PTCA, which seems to be associated with a higher risk for restenosis. Second, a dilatation of the proximal LAD often involves the origin of the vessel and vessel branch points, and this factor also appears to be associated with an increased risk of restenosis. Third, the proximal LAD is well-recognized to develop "localized stenosis." Whether the same underlying mechanisms may predispose a patient to recurrence of lesions after angioplasty is unknown but well-conceivable.

Because balloon/artery mismatch was not identified as a predictor for restenosis in a group of patients with multilesion coronary angioplasty, Vandormael et al[13] suggested that the different anatomic and structural features of the proximal segment of the LAD compared with those of the proximal segment of the right coronary artery or LC may be responsible for the observation that dilatation of the proximal LAD is an independent risk factor for restenosis.

According to Califf et al,[3] 1 of the methodologic caveats for an increased rate of restenosis in the proximal LAD was that an ischemic response to exercise testing was more likely to be seen with proximal LAD lesions, thereby increasing the chance of preferential detection unless angiographic follow-up was complete. Also, a larger diameter of this vessel may have increased the risk that a satisfactory initial result was not achieved in earlier series, especially before the recent development of larger balloons to approach large vessels.

In the present study, no significant difference in the restenosis rate was found among the 3 major coronary arteries ($p = 0.22$) or the 9 coronary artery segments ($p = 0.06$) selected for the purpose of analysis. Our results contradict the earlier observations of Leimgruber and Califf and their coworkers that the proximal LAD is the largest vessel. In the present study almost every segment of the right coronary artery has a larger diameter than the proximal LAD. An explanation for this discrepancy may be the differences in patient populations; availability of different balloon sizes (with diameters <2.0 mm as compared with those in the early days of PTCA when only balloon sizes of 3.7 mm were available) for dilatation may have affected PTCA of the proximal LAD. Another argument put forth in the early years that there was a mismatch between balloon catheters and proximal LAD is no longer valid, because in the present study, all patients underwent PTCA between December 1987 and December 1989 so that in all cases matched balloons were available. The differences in restenosis rates reported by these investigators are probably more related to the biased and incomplete angiographic follow-ups of these studies. In contrast, the present study has a 91% angiographic follow-up rate, and so the biased selection of symptomatic versus asymptomatic patients is virtually ruled out.

Definition of restenosis: The definition of restenosis has been the subject of much debate.[4] Of the different restenosis criteria proposed, >50% diameter stenosis at follow-up angiography is the most frequently used to assess restenosis, because physiologic measurements have shown that the threshold for chest pain is near a reduction of 50% of the lumen of a normal vessel.[22] This definition was applied to our data. However, earlier studies have shown that the reference diameter can be involved in the dilatation process so that the % diameter stenosis could underestimate the change in the severity of a stenosis after PTCA.[26] Furthermore, the 50% diameter stenosis criterion at follow-up reveals nothing about the way the lesion has behaved since the PTCA procedure. We have previously shown that a change ≥0.72 mm in minimal luminal diameter is an appropriate method to assess intimal hyperplasia after coronary PTCA.[5,20,27] However, this criterion was historically assessed in vessels with an average reference diameter of 3.7 mm.[5,20] Therefore, it should be applied to vessels of comparable reference diameter; it is unlikely to have a decrease ≥0.72 mm in coronary segments with a reference diameter of 2 mm, and a minimal luminal diameter of 1.4 mm. In other words, criteria based on the absolute change in minimal luminal diameter are limited because they make no attempt to relate the extent of the restenosis process to the size of the vessel. To circumvent this limitation it was proposed to use the change in minimal luminal diameter from after PTCA to follow-up, normalized for the reference diameter (relative loss). This sliding scale criterion that adjusts for vessel size allows for regional assessment of the extent of the restenosis phenomenon in the entire coronary tree. No difference in relative loss among the 3 major coronary arteries ($p = 0.13$) or the coronary segments could be observed ($p = 0.19$). Restenosis should thus be viewed as a ubiquitous phenomenon that is inducible to the same extent in every segment of the coronary tree. It must be emphasized that the relative gain (change in minimal luminal diameter from before to after PTCA, normalized for the reference diameter) and thus the stimulus for restenosis[28] were similar in every segment of the coronary tree.

Because the subdivision of the American Heart Association-coronary segments is somewhat arbitrary in that vessels of different diameters are grouped together, we reanalyzed the data by stratifying the lesions according to their reference diameters. Table IV lists the results. It appears that the larger the reference diameter is before PTCA, the smaller the relative loss is at follow-up; vice versa, the greatest value of relative loss is observed in the smaller vessels. This may be explained by oversizing of the balloon in these vessels. However, if the restenosis criterion of >50% diameter stenosis is used, then similar restenosis rates are found.

Potential limitation of the study: Our study population consisted mainly of patients with 1 dilatation site; 1,044 patients had 1 dilatation site, and 190 underwent dilatation of ≥2 sites. The high incidence of 1 dilatation site reflects the fact that the study population included in these 2 trials consisted predominantly of patients with 1-vessel disease, so that our findings may not be extrapolated to a population with multivessel disease. Nevertheless, in the subset of 93 patients with multivessel dilatation, the overall restenosis rate per lesion was also 31%. However, the relative gain and loss observed in

patients with 1- and 2-vessel dilatations differed statistically; a relative gain of 0.30 ± 0.16 was seen for 1-vessel dilatation versus 0.27 ± 0.16 for 2-vessel dilatation ($p < 0.04$), and a relative loss of 0.12 ± 0.21 for 1-vessel dilatation versus 0.08 ± 0.20 for 2-vessel dilatation ($p < 0.02$). Thus, in the population with 2-vessel dilatation, a reduced gain is associated with a reduced loss consistent with the concept that PTCA operators are less aggressive in their dilating strategy.

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Spectral Analysis of Heart Rate Dynamics in Elderly Persons with Postprandial Hypotension

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Prior studies suggest that postprandial hypotension in elderly persons may be due to defective sympathetic nervous system activation. We examined autonomic control of heart rate (HR) after a meal using spectral analysis of HR data in 13 old (89 ± 6 years) and 7 young (24 ± 4 years) subjects. Total spectral power, an index of overall HR variability, was calculated for the frequency band between 0.01 and 0.40 Hz. Relatively low-frequency power, associated with sympathetic nervous system and baroreflex activation, was calculated for the 0.01 to 0.15 Hz band. High-frequency power, representing parasympathetic influences on HR, was calculated for the 0.15 to 0.40 Hz band.

Mean arterial blood pressure declined 27 ± 8 mm Hg by 60 minutes after the meal in elderly subjects, compared with 9 ± 8 mm Hg in young subjects ($p \leq 0.0001$, young vs old). The mean change in low-frequency HR power from 30 to 50 minutes after the meal was +19.4 ± 25.3 U in young subjects versus −0.1 ± 1.5 U in old subjects ($p \leq 0.02$). Mean change in total power was also greater in young (19.0 ± 26.6 U) subjects compared with old subjects (0.0 ± 1.6 U, $p \leq 0.02$). Mean ratio of low:high-frequency power increased 3.1 ± 3.3 U in young subjects vs 0.5 ± 2.7 U in old subjects ($p \leq 0.01$).

The increase in low-frequency HR power and in the low:high frequency band ratio in young subjects is consistent with sympathetic activation in the postprandial period. Absence of this finding in elderly subjects with postprandial hypotension is consistent with defective baroreflex compensation after a meal.

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Postprandial hypotension is frequently observed in elderly persons[1–5] and in patients with autonomic insufficiency.[6,7] Although its mechanism has not been fully elucidated, a previous study in our laboratory demonstrated failure to sustain postprandial elevations in plasma norepinephrine in elderly subjects with postprandial hypotension and syncope.[8] These data suggest that postprandial hypotension may be due to defective sympathetic nervous system activation after a meal.

Power spectral analysis of cardiac interbeat interval dynamics provides a noninvasive method of estimating sympathetic and parasympathetic contributions to heart rate (HR) variability.[9–13] This technique, using the fast-Fourier transform, decomposes HR fluctuations into their component frequencies. The power of HR fluctuations in physiologically relevant frequency bands can then be computed. The high-frequency band (0.15 to 0.40 Hz) reflects vagal input to the sinus node, whereas the relatively low-frequency band (0.01 to 0.15 Hz) primarily reflects sympathetic input associated with the baroreflex.

Prior studies using spectral analysis techniques have demonstrated a marked decline in high- and low-frequency components of HR variability in healthy elderly subjects during supine rest.[14–16] Two recent studies[13,17] of healthy young subjects have shown an increase in the amplitude of low-frequency fluctuations from as early as 20 minutes to as late as 90 minutes after a standardized meal. These findings suggest a postprandial increase in sympathetic activity in young persons with normal blood pressure (BP) homeostasis. The present study investigates the dynamics of beat-to-beat HR fluctuations after a meal in elderly people at risk of postprandial hypotension. We hypothesized that, in contrast to healthy young subjects, elderly subjects would have blunted sympathetic activation after a meal, evidenced by a reduction in relatively low-frequency HR fluctuations.

METHODS

Ambulatory electrocardiographic and systemic arterial BP data were acquired during a prospective study investigating cardiovascular responses to common daily activities.[18] Selection criteria for the study included: normal sinus rhythm, adequate technical quality of the ambulatory electrocardiographic signal and stable medical condition.

Subjects: Two groups of subjects were studied: 13 ambulatory elderly residents of the Hebrew Rehabilitation Center for Aged, an academic multilevel chronic care facility, and 7 healthy young volunteers recruited from the local community. All subjects provided in-

TABLE I Characteristics and Spectral Power of Elderly and Young Subjects

	Elderly (n = 13)	Young (n = 7)	
Demographics			
Age (year ± SD)	89 ± 6	24 ± 4	
Sex (women:men)	7:6	4:3	
Medical history/medications			
Diabetes mellitus	4	0	
Systemic hypertension	8	0	
Cardiac disease	9	0	
Parkinson's disease	1	0	
Cerebrovascular disease	3	0	
Syncope	2	0	
Digoxin	2	0	
Antihypertensive*	7	0	
Diuretic	2	0	
Calcium antagonists	4	0	
β blocker	1	0	
Insulin	1	0	
Nonsteroidal analgesic	6	0	
Baseline cardiovascular characteristics	Mean (±SD)		p Value
Heart rate (beats/min)	65 (12)	57 (6)	
Mean arterial BP (mm Hg)	104 (13)	74 (3)	≤0.05
Spectral power†			
Total power (0.01–0.40 Hz)	6.8 (5)	48.3 (13)	≤0.05
Low power (0.01–0.15 Hz)	5.3 (4)	36.7 (9)	≤0.05
High power (0.15–0.40 Hz)	1.5 (2)	11.6 (10)	≤0.05
Low:high power ratio	6.8 (6)	5.9 (7)	

*Not including diuretics, β blockers or calcium antagonists.
†Power in different bands is given in arbitrary units.
BP = blood pressure.

formed consent before the study. Subject characteristics are displayed in Table I.

Meal study protocol: All subjects fasted beginning at midnight before the study and all medications were held for ≥12 hours before the study. HR was recorded continuously using an ambulatory electrocardiographic recorder (Del Mar Avionics, Irvine, California). All subjects followed the same protocol. Brachial artery cuff BP was recorded at 5-minute intervals during the study using an automated oscillometric device (Ivac Vital Check, model 4000). Basal recordings were taken during the 30-minute period before rising while the subjects rested supine (Table I). After personal care needs had been attended to, all subjects sat quietly in a chair. BP and HR before the meal were recorded as the average of 2 readings taken 5 minutes apart before eating. The breakfast meal consisted of cereal, 112 g of milk, 1 to 2 slices of toast with margarine, 140 to 196 g of orange juice and 1 cup of decaffeinated coffee. The meal was consumed within 15 minutes by all subjects. Sitting BP was recorded at 5-minute intervals from 30 to 60 minutes after the start of the meal. Mean arterial BP was estimated as one-third pulse pressure + diastolic pressure.

Heart rate spectral analysis: Tape-recorded electrocardiograms were digitized at 123 Hz using a Marquette Series 8000 Holter analysis system. The digitized HR data were then annotated using an automated arrhythmia detection algorithm and the beat annotations

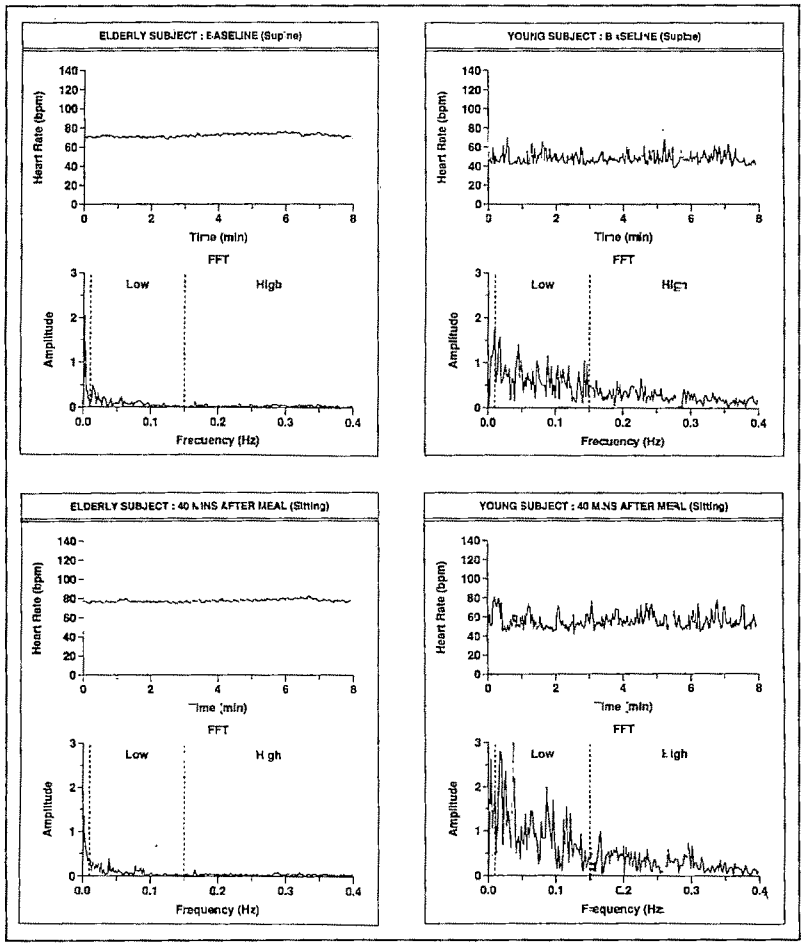


FIGURE 1. ***Upper*** **sections of each** ***panel*** **display representative heart rate (HR) time series;** ***lower*** **sections display corresponding fast Fourier transforms (FFT). Data from 1 elderly** ***(left)*** **and 1 young** ***(right)*** **subject are shown at baseline** ***(upper panels)*** **and 40 minutes after the meal** ***(lower panels).*** **The young subject demonstrates an increase in low-frequency HR fluctuations after the meal. In contrast, the elderly subject has attenuated HR fluctuations at baseline with no change after the meal. Spectral amplitude is given in arbitrary linear units.**

were verified manually. Eight-minute sections were selected during the initial supine basal period, and beginning at 30, 40 and 50 minutes after breakfast while the subjects were sitting in a chair.

Instantaneous HRs during these 8-minute segments were obtained by resampling the interbeat intervals at 2 Hz. These HR time series were then processed by a fast-Fourier transform algorithm as previously described.[14] This yielded a 512-point power spectrum for the 0.01 to 1.0 Hz frequency band. Total power was measured for the frequency band between 0.01 and 0.4 Hz; relatively low- and high-frequency powers were measured for the 0.01 to 0.15 and 0.15 to 0.4 Hz bands, respectively (Figure 1). The ratio of the low- to high-frequency power was calculated during baseline supine rest and during the 3 postprandial time periods. This ratio provides an index of the balance between relatively low (predominately sympathetic) and high (parasympathetic) frequency HR fluctuations.

Statistical analysis: The Student's *t* test and the nonparametric Wilcoxon signed rank test (to adjust for differences in sample variances) were used for between-group comparisons and repeated-measures analysis of variance was used for within-group comparisons. Statistical analysis was done using the SPSS-X and SAS software programs. Spectral power is reported in arbitrary units. Unless otherwise indicated values are reported as mean ± standard deviation. Statistical significance is defined as a $p \leq 0.05$.

RESULTS

Baseline characteristics: Clinical and baseline cardiovascular characteristics of the subjects are summarized in Table I. The mean age was 24 ± 4 and 89 ± 6

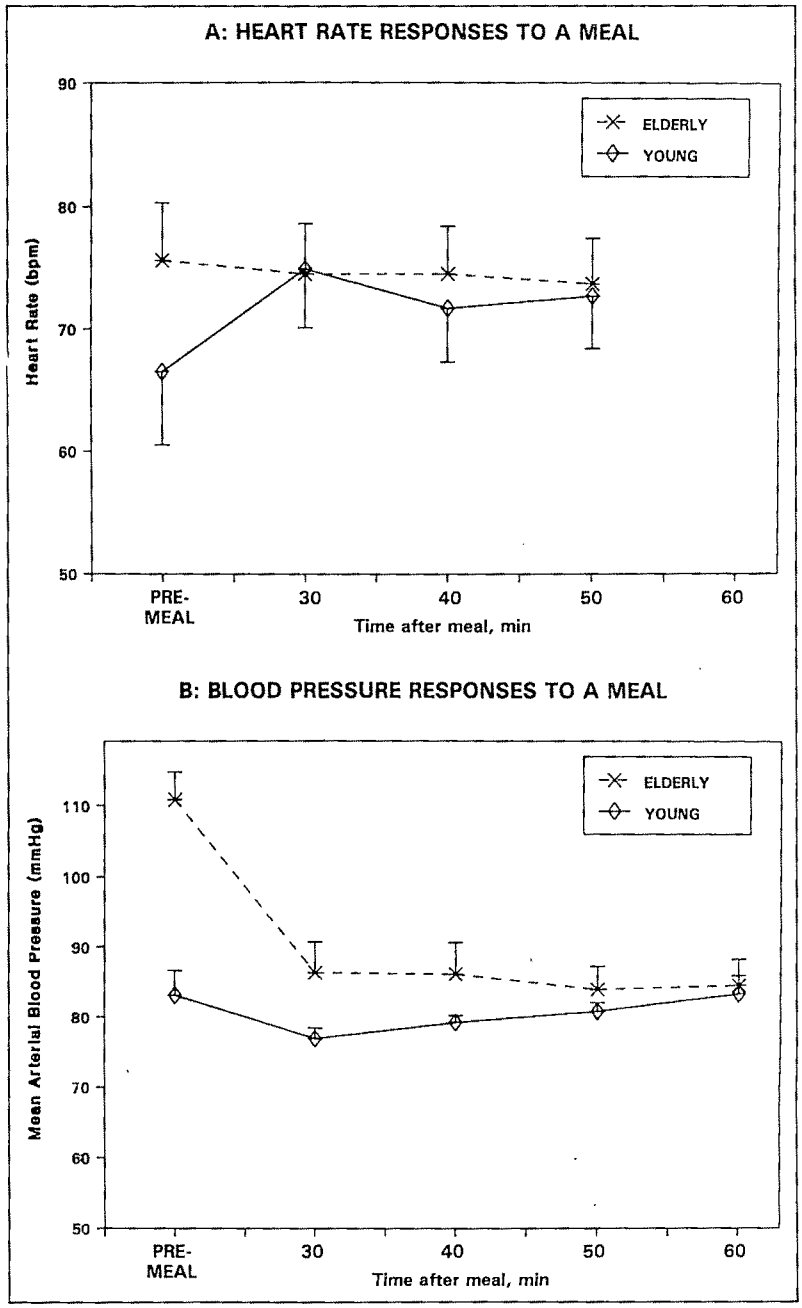


FIGURE 2. *A*, change in heart rate after the meal for young *(diamonds)* and elderly *(crosses)* subjects. There was no significant difference between the groups. *B*, change in mean arterial blood pressure after the meal for young *(diamonds)* and elderly *(crosses)* subjects. Elderly subjects have higher premeal blood pressure values versus those in the young ($p \leq 0.05$). Furthermore, there was a significant decrease ($p \leq 0.05$) in mean arterial pressure at 30 minutes after the meal in the elderly but not in the young subjects.

years for the young and old groups, respectively. Elderly subjects had multiple chronic illnesses, all of which were well controlled at the time of the study. There was no significant difference in mean HR at rest. Mean arterial BP was significantly higher ($p \leq 0.05$) in elderly subjects.

Overall baseline HR variability, measured by total HR power, and the absolute power of all frequency bands was significantly greater ($p \leq 0.05$) in young than in elderly subjects. However, the ratio of relatively low- to high-frequency power was not different between the 2 groups during the supine baseline period (Table I).

Cardiovascular response to a meal: HR and mean BP responses to a meal are shown in Figure 2 for the elderly and young groups of subjects. Mean HR before the meal was 75 ± 17 beats/min for the elderly and 67 ± 16 beats/min for the young subjects. Neither group exhibited statistically significant postprandial changes in mean HR. However, elderly subjects had a large postprandial reduction in mean arterial BP (decrease of 27 ± 8 mm Hg by 60 minutes; $p \leq 0.05$ for intragroup change) in contrast to young subjects (decrease of 9 ± 8 mm Hg by 60 minutes, $p \leq 0.05$ for intragroup change; $p \leq 0.0001$ for old compared with young). None of the subjects experienced dizziness or syncope after the meal.

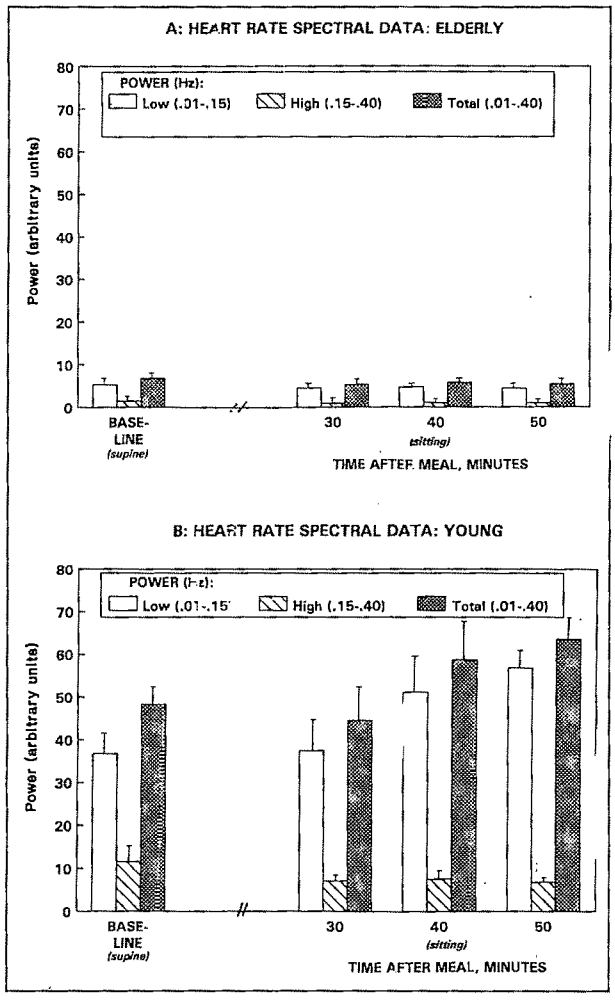


FIGURE 3. Baseline and postprandial spectral power data for elderly *(A)* and young *(B)* subjects. Mean change from 30 to 50 minutes after the meal in total- and low-frequency power is significantly greater for young than elderly subjects ($p \leq 0.02$).

Heart rate spectral response to the meal: To compare changes in spectral power after the meal we examined data from the 30- to 50-minute time period for young and old subjects while they remained seated. These data points coincided with the time of maximal BP reduction in elderly subjects. Representative HR time series and frequency spectra for 1 young and 1 elderly subject before and 40 minutes after the meal are shown in Figure 1.

The change in low-frequency spectral power from 30 to 50 minutes after the meal was greater in young (+19.4 ± 25.3 U) than in old subjects (−0.1 ± 1.5 U) ($p \leq 0.02$). The young also demonstrated a greater change in total spectral power after the meal, 19.0 ± 26.6 U in young vs 0.0 ± 1.6 U in old subjects ($p \leq 0.02$). There was no significant change in high-frequency power in either group (+0.1 ± 0.2 vs −0.4 ± 3.2 U for old versus young subjects, respectively). However, the change in the low:high-frequency power ratio was significantly greater ($p \leq 0.01$) in young (3.1 ± 3.3) than in old (−0.5 ± 2.7) subjects, reflecting the increase in low-frequency power observed in the young subjects.

Figure 3 shows the change in spectral power over time in the old and young subjects. When analyzed individually, 6 of the 7 young subjects increased their low and total HR power from 30 to 50 minutes postprandially. The remaining subject did demonstrate an increase in low-frequency power from 30 to 40 minutes after the meal but then showed a decline in power from 40 to 50 minutes.

Effect of clinical conditions in elderly subjects: Subgroup analyses did not reveal any significant differences in baseline HR spectral characteristics or in HR responses to the meal in elderly subjects with diabetes mellitus, hypertension, previous history of cardiac disease or use of antihypertensive medications, calcium antagonists, diuretics or nonsteroidal analgesics compared with elderly subjects without these conditions or medications.

DISCUSSION

This study demonstrates an increase in relatively low-frequency HR fluctuations during the postprandial period in healthy young subjects. In contrast, elderly subjects with chronic illnesses had little change in low-frequency HR power after the meal, despite marked reductions in BP. These data are consistent with the hypothesis that splanchnic pooling of blood after a meal activates baroreflexes and increases sympathetic modulation of HR in healthy young subjects. In contrast, elderly subjects with postprandial hypotension appear to have blunted sympathetic control of HR, which may contribute to their impaired postprandial BP homeostasis.

Postprandial hypotension: clinical importance and possible mechanisms: The pathophysiologic mechanisms involved in postprandial hypotension are not fully understood. In young subjects a standardized mixed meal results in an increase in HR and cardiac output, which appears to provide adequate protection against

hypotension.[19,20] In addition, the increase in plasma norepinephrine levels after a standard meal seen in healthy young and elderly subjects provides neurohumoral evidence of sympathetic activation in the postprandial period.[8] In contrast, elderly subjects with postprandial hypotension and syncope have an initial increase in plasma norepinephrine after a meal similar to the healthy elderly, but this response is not sustained.[8] In these subjects, plasma norepinephrine decreases to basal levels between 30 and 90 minutes after the meal — paralleling the postprandial decrease in BP observed in these subjects. This suggests that elderly subjects with postprandial hypotension are unable to maintain sympathetic nervous system activation after a meal. In addition to possible failure of sympathetic activation after a meal, our findings are consistent with impaired HR response to sympathetic stimulation.[21-23]

Spectral analysis of heart rate dynamics: Spectral analysis of HR variability has not been previously used in elderly subjects after a meal. Prior studies using HR spectral analysis techniques in healthy young subjects have demonstrated an increase in relatively low-frequency power as early as 20 minutes[17] to as late as 90 minutes[13] after a meal. These results are consistent with the increase in low-frequency power observed in our young subjects and may reflect postprandial sympathetic activation.

Previous studies[13,17] in healthy subjects have also demonstrated a decline in the high-frequency components of the HR power spectrum, implying a decline in parasympathetic activity after a meal. In contrast, there was no significant change in the high-frequency HR spectral power in our subjects. There are at least 3 possible explanations for the apparent disparity among studies. First, unlike Hayano et al,[13] we did not use metronomic breathing to enhance the high-frequency, vagally mediated respiratory sinus arrhythmia. Second, the first segment of data available for analysis in our study began at 30 minutes postprandially, precluding earlier assessment of HR response to meals when high-frequency activation may occur. Finally, upright posture may have augmented the sympathetic and decreased the parasympathetic components of HR variability in our subjects.

There are several limitations to this study. The elderly subjects were institutionalized and had multiple chronic illnesses. Although certain diseases and medications may influence HR variability, individual elderly subjects demonstrated similar impairments in low-frequency HR variability after the meal, regardless of the presence or absence of these conditions. In addition, our sample of young subjects was relatively small; therefore, the absence of a high-frequency power change could represent a type II error. It will be useful in future studies to study healthy elderly persons to monitor longer pre- and postprandial time periods to further evaluate the immediate and delayed effects of meals on cardiovascular homeostasis, to monitor BP continuously and to measure plasma catecholamines.

Despite these limitations, this is the first study to demonstrate the failure of certain elderly subjects to augment relatively low-frequency HR fluctuations after a meal. This finding may be related to the pathophysiology of postprandial hypotension. Furthermore, we have shown spectral analysis to be a useful tool for quantitative assessment of HR dynamics in the postprandial period. This technique may be particularly valuable in elderly subjects who are prone to hypotension after meals and in whom more invasive monitoring may not be practical or safe.

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Pharmacology of the Class III Antiarrhythmic Agent Sematilide in Patients with Arrhythmias

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Sematilide, a close structural analog of N-acetylprocainamide, prolongs cardiac action potentials in vitro, whereas it does not depress maximum action potential upstroke slope, a "class III" action. This report outlines an evaluation of the clinical pharmacologic actions of sematilide in 14 patients with chronic high-frequency nonsustained ventricular arrhythmias. In all, 36 intravenous infusions (range 0.15 to 1.5 mg/kg over 15 minutes) were administered in a dose-ranging, placebo-controlled study design. Sematilide prolonged rate-corrected QT (QTc) in a dose- and concentration-related fashion, did not alter PR or QRS, and slowed heart rate at high concentrations (≥2 μg/ml). The relations between dose and total area under the time-concentration curve, dose and peak plasma concentration, and peak plasma concentration and increase in QTc were linear ($r = 0.66$ to 0.92; $p < 0.001$). QTc increases of ≅ 25% were seen at plasma concentrations of ≅ 2.0 μg/ml. The mean elimination half-life (± SD) was 3.6 ± 0.8 hours, and most of a dose (77 ± 13%) was recovered unchanged in the urine. Plasma concentrations ≥0.8 μg/ml suppressed arrhythmias (5 patients) or aggravated them (3), including 1 patient who needed cardioversion for an episode of torsades de pointes (2.7 μg/ml). Thus, sematilide exerts class III actions in patients. Further studies to evaluate the role of this antiarrhythmic mode of action should be conducted at doses designed to limit QTc increases.

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Most currently used antiarrhythmic agents act by blocking cardiac sodium channels, a "class I" action.[1] Selective action potential prolongation without depression of the fast inward sodium current was proposed as an alternate ("class III") antiarrhythmic mode of action.[1,2] Currently available action potential prolonging agents such as quinidine, procainamide, disopyramide, amiodarone and bretylium do not exert "pure" class III actions, because each produces other electrophysiologic effects, such as sodium channel block or autonomic actions. The class III action has a number of theoretical and experimental attractions, including efficacy in experimental tachyarrhythmias,[3,4] enhanced cardiac contractility[5] and facilitated defibrillation.[6] A liability is the occasional patient who develops marked action potential (and resultant QT) and torsades de pointes.[7–10]

N-acetylation of the aromatic amine of procainamide results in a major metabolite N-acetylprocainamide (NAPA), a class III compound that retains the action potential prolonging effect of the parent drug, but is several orders of magnitude less potent a sodium channel blocker.[11,12] NAPA exerts antiarrhythmic effects and does not induce a lupus-like syndrome, but is not well-tolerated because of gastrointestinal side effects.[13–15] Sematilide is a close structural analog of NAPA with a paramethylsulfonamide (like sotalol) instead of a para N-acetyl group (Figure 1). Sematilide prolongs action potentials in canine cardiac Purkinje fibers and does not depress maximum velocity.[16] In this study, we report an initial evaluation of the pharmacologic effects of sematilide on patients with chronic, nonsustained ventricular arrhythmias.

METHODS

Protocol overview: Eligible patients were identified, and chronic antiarrhythmic therapy (if any) was stopped for ≥5 elimination half-lives in the outpatient setting. Outpatient screening was then performed, which included history, physical examination, chest x-ray, urinalysis, biochemical and hematologic screening studies, and 48-hour Holter monitoring. Patients meeting inclusion criteria and not having any exclusion criteria were then admitted to the clinical research center at Vanderbilt University Hospital (n = 11) or to the cardiac center at Creighton University Hospital (n = 3) for a 5-day stay (Figure 2). On days 1, 2, 3 and 4, patients received a 15-minute infusion of saline solution (day 1) or of sematilide (days 2 to 4). After completion of data collection and the last infusion, chronic antiarrhythmic therapy (if any) was restarted, and the patients were discharged. The full protocol was approved by the com-

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mittees for the protection of human subjects at the respective institutions, and informed consent was obtained from all patients before discontinuing outpatient antiarrhythmic therapy.

Inclusion/exclusion criteria: Patients aged 18 to 65 years and known to have chronic, high-frequency, nonsustained ventricular arrhythmias were candidates for this study. A minimum of 60 ventricular premature complexes (VPCs) per hour and no ventricular tachycardia run >20 beats were required on the 48-hour screening Holter monitor before admission.

Exclusion criteria were: (1) woman of childbearing potential; (2) unstable or frequent angina with no exertion; (3) myocardial infarction within the past 3 months; (4) congestive heart failure (New York Heart Association class II to IV) or cardiomegaly on chest x-ray; (5) impairment of renal function (serum creatinine ≥1.5 mg/dl); (6) impairment of hepatic function (serum transaminases >20% above the upper limits of normal); (7) serum potassium <3.5 or >5.5 mEq/liter, or serum magnesium <1.5 or >2.5 mEq/liter; (8) ventricular preexcitation or permanent pacemaker; (9) PR >250 ms, 2- or 3-degree atrioventricular block, left bundle branch or bifasicular block, or known sinus node disease; (10) symptomatic bradycardia (<45/min) or hypotension (standing systolic blood pressure <90 mmHg); (11) known allergy to procainamide, NAPA or sotalol; (12) other serious systemic disease; (13) history of psychotic illness, alcoholism or drug abuse; (14) amiodarone therapy within the previous 3 months; and (15) concomitant treatment with other antiarrhythmic drugs (including digitalis, β blockers and calcium antagonists), β_2 agonists or sympathomimetics, antacids, H_2 antagonists, tricyclic antidepressants, monoamine oxidase inhibitors or benzodiazepines.

Study procedure: On each infusion day (days 1 to 4) patients fasted overnight and were brought to a treatment room in the morning. Intravenous lines were inserted in both arms, 1 for drug or saline solution infusion, and the second for blood withdrawal. Saline solution or drug was administered intravenously over 15 minutes by antecubital vein using an infusion pump. In each subject, the first infusion was saline solution and the remaining 3 infusions were sematilide hydrochloride at increasing dosages (Figure 2). Initial patients entered into the trial received low doses (0.15, 0.2 and 0.3 mg/kg). If no adverse effects or other dose-limiting end points (see later) were observed, the next group of patients received higher dosages (0.3, 0.5 and 0.7 mg/kg). Similarly, the last group of patients was scheduled to receive higher dosages (0.7, 1.0 and 1.5 mg/kg). The highest dose in group A and B patients corresponded to the initial dose in group B and C patients, respectively.

Frank orthogonal vectorcardiographic leads (Hewlett-Packard electrocardiograph recorder model 7754A) or standard electrocardiograms were obtained at a paper speed of 50 mm/s before infusion, and at 5, 10, 15, 17, 20, 25 and 35 minutes and 1, 1.5, 2, 3, 4, 6, 9, 12 and 18 hours after the beginning of each infusion. Blood samples (10 ml) were obtained for subsequent analysis of plasma sematilide at the same times on days 2 to 4. Twenty-four-hour urine samples were collected on day 1 (for creatinine clearance) and on infusion days 2 to 4 for measurement of urinary recovery of sematilide.

Infusions were to be interrupted if any of the following occurred: QT prolonged by >40%; PR or QRS prolonged by >50%; new conduction disturbances (2- or 3-degree atrioventricular block, sinus arrest, or left bundle branch or bifasicular block); new arrhythmias such as atrial fibrillation; sinus tachycardia (>140/min) or bradycardia (<40/min); or other severe adverse reaction. In this study, no infusion was interrupted for any of these reasons. In each patient, a subsequent dose of sematilide was administered unless 1 of the following occurred: (1) QTc increased by >40% compared to that with placebo; or (2) proarrhythmic effect, defined as a new development of sustained tachycardia or an increase in VPCs using the criteria adopted in the Cardiac Arrhythmia Pilot Study[17]: Ln (y) ≥3.118 + 0.646 Ln (x), where y is the hourly frequency of VPCs during treatment, and x is the hourly frequency of VPCs during placebo. On-line microprocessor-based systems were used to assess whether the arrhythmia-provoking end point for dosing had been reached before the next infusion.

Data analysis: Plasma and urine concentrations of sematilide were analyzed by high-performance liquid chromatography. The lower limit of assay sensitivity for a 10 ml plasma sample was 0.01 μg/ml. Electrocar-

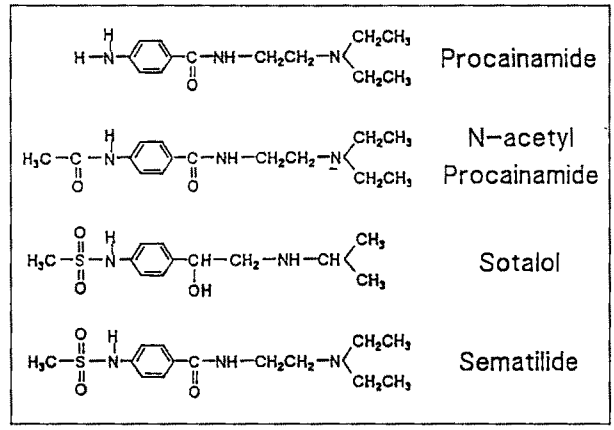


FIGURE 1. Structures of procainamide, N-acetylprocainamide, sotalol and sematilide.

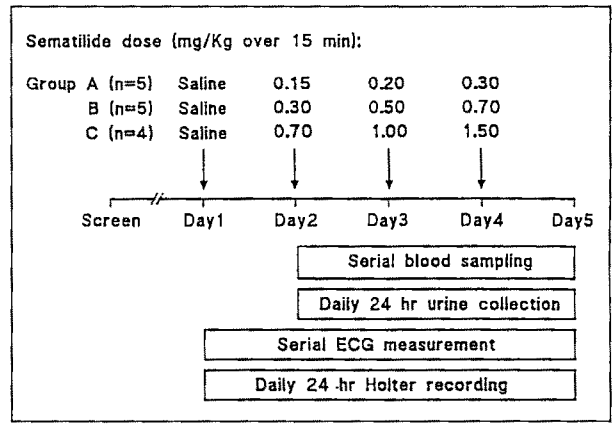


FIGURE 2. Protocol design. ECG = electrocardiographic.

TABLE I Patient Characteristics

Age (yr) & Sex	VPCs/Hour	Diagnosis
Group A: 0.15, 0.20 and 0.30 mg/kg of Sematilide		
39 M	34	MVP
42 M	1,780	CAD
58 M	54	CAD
58 M	2,720	CAD
63 M	62	CAD
Group B: 0.30, 0.50 and 0.70 mg/kg of Sematilide		
52 F	458	MVP
56 M	1,049	MVP
57 M	1,347	Idiopathic cardiomyopathy
59 M	1,297	CAD
60 M	1,179	No identifiable heart disease
Group C: 0.70, 1.0 and 1.5 mg/kg of Sematilide		
42 F	155	No identifiable heart disease
56 F	246	No identifiable heart disease
59 M	830	CAD
65 M	1 681	Hypertensive heart disease

Patients listed by ascending age within study groups.
CAD = coronary artery disease; MVP = mitral valve prolapse; VPCs = ventricular premature complexes.

diographic intervals (PR, QRS, QT and RR) were determined by averaging 5 consecutive beats from the rhythm strip record. Rate-corrected QT (QTc) was determined by the Bazett formula ($QTc = QT/\sqrt{RR}$).

Compartmental and noncompartmental approaches were used to analyze the disposition kinetics of sematilide. Multicompartment models were to fit plasma concentration-time data, weighted by $(1/y^{1.3})$,[18] using the program EDFAST.[19] The total area under the time-concentration curve was calculated by the trapezoidal (ascending) and log trapezoidal (descending) rules, with extrapolation to infinity. Clearance was calculated as the dose (expressed as mg of base throughout) divided by the area under the curve.[20] Renal clearance was calculated as the renal recovery in 24 hours (base) divided by the area under the curve. The steady-state volume of distribution was calculated[21] by the formula[32]: dose · (mean residence time-infusion time/2)/(area under curve).

Cardiac rhythm was monitored throughout the patient's stay in the hospital, recorded on FM tape and analyzed by a commercial template-matching scheme. For the purposes of stratifying transient antiarrhythmic or arrhythmogenic responses, the following scheme was adopted in this report. Arrhythmia frequency was analyzed in 10-minute blocks and compared with data recorded before infusion. An antiarrhythmic response was defined as ≥90% decrease in the 10-minute VPC frequencies, confirmed by return toward baseline after infusion. Other response classifications were >100% increase during infusion (followed by a return to baseline), development of new sustained tachyarrhythmias, and no change.

QTc intervals were calculated as percentage of data recorded before infusion and were compared with data recorded during placebo infusion using the Sheffé multiple contrast and additivity test to include both the effect of time after infusion and of sematilide dosage. Linear regression was used to assess the relations between sematilide dose and concentration, and sematilide plasma concentration and change in electrocardiographic intervals. Two-way analysis of variance was used to assess the significance of changes in electrocardiographic intervals over time; if the null hypothesis of equal means could be rejected at the 0.05 level, the Scheffé test was used for pairwise comparisons. All values are presented as mean ± 1 standard deviation.

RESULTS

Patient characteristics: Fourteen patients participated in this study (Table I). In all, 36 complete infusions were administered. In 2 patients, arrhythmia aggravation developed, and only 1 and 2 infusions were performed, respectively. One patient had >40% QTc prolongation after the first infusion, and the next 2 dosages were not administered. Finally, 1 infusion was terminated after approximately 8 minutes, because of an inability to withdraw plasma samples.

Pharmacokinetics: An example of 2- and 3-compartment fits to plasma concentration-time data is shown in Figure 3. Overall, a 3-compartment model was

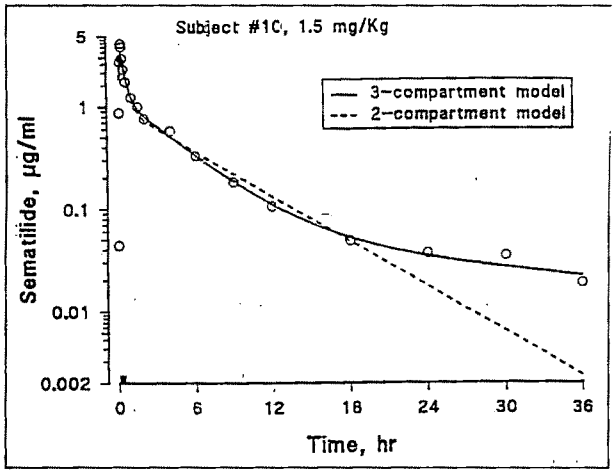


FIGURE 3. Comparison of 2- and 3-compartment models in 1 subject after 1.5 mg/kg of sematilide.

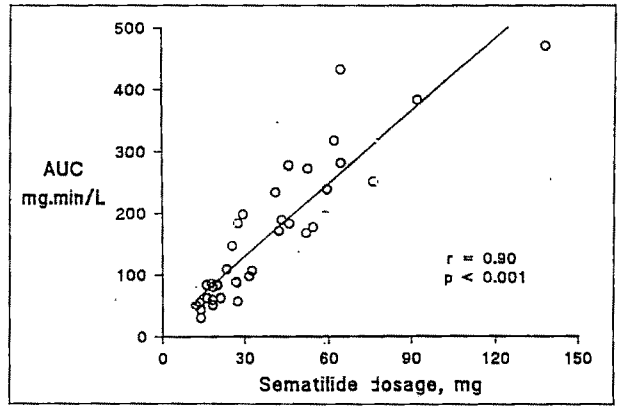


FIGURE 4. Relation between sematilide dose and area under time-concentration curve (AUC).

superior to a 2-compartment one in 14 of 36 cases. The elimination (terminal phase) half-life was 3.6 ± 0.8 hours (range 2.3 to 5.5). Most of an administered dose (77 ± 13%) was recovered unchanged in the urine. Systemic clearance was 256 ± 64 ml/min, renal clearance was 195 ± 67 ml/min, and the steady-state volume of distribution was 78 ± 18 liters. The relation between dose and area under the curve was linear (Figure 4), indicating nonsaturable kinetics in this dose range. Creatinine clearances were all in the normal range (125 ± 36 ml/min) in this group of patients.

Pharmacodynamics: QTc interval prolonged as a function of time during and after an infusion and then returned to baseline (Figure 5). Peak QTc prolongation was seen within 10 to 15 minutes after the end of the infusion, indicating no substantial hysteresis, and QTc returned to or near baseline within 1 elimination half-life. As shown in Figure 6, PR and QRS were unaffected by sematilide; as described later, heart rate slowed slightly at high concentrations.

An example of an antiarrhythmic response to sematilide is shown in Figure 7. With infusion of placebo, no change in VPC frequency was observed. However, with infusions of 0.3, 0.5 and 0.7 mg/kg, arrhythmias were transiently suppressed and then returned toward baseline. No increases or decreases in VPC frequency (defined previously) were observed in the 14 placebo infusions. In 1 subject, arrhythmia frequency immediately before and during infusion was <1 VPC/min, precluding detection of any antiarrhythmic response. Another patient had a malfunctioning Holter recording during 1 sematilide infusion. Antiarrhythmic responses were seen in 14 of the remaining 32 drug infusions. These responses occurred in 5 patients over the full dose range evaluated (0.15 to 1.5 mg/kg). No change in arrhythmia frequency was seen in 12 of 32 infusions. In the remaining 6 drug infusions, arrhythmias were transiently increased by sematilide. In 1 subject, infusions of 0.3, 0.5 and 0.7 mg/kg were all associated with a transient

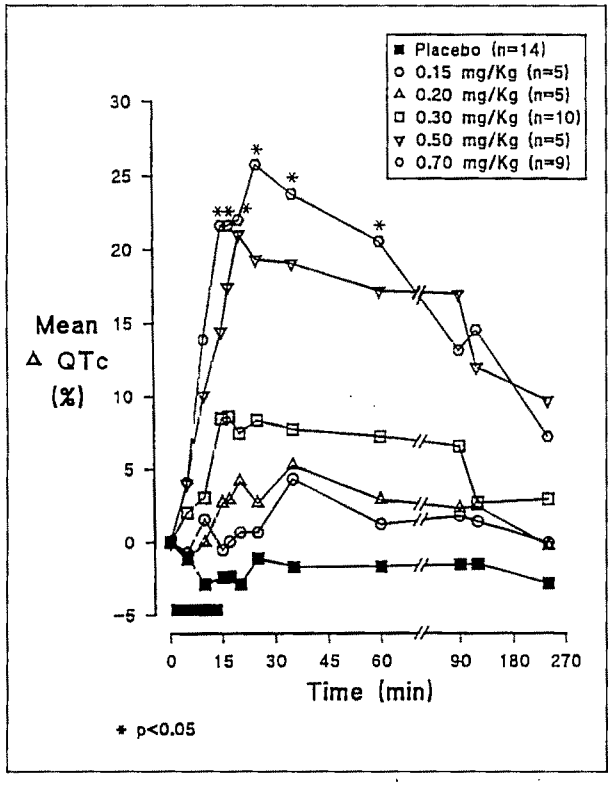


FIGURE 5. Relation between time after beginning of 15-minute infusion *(black bar)* and change in rate-corrected QT (Δ QTc), as function of dose. Standard error bars are omitted for clarity, but levels of statistical significance are indicated.

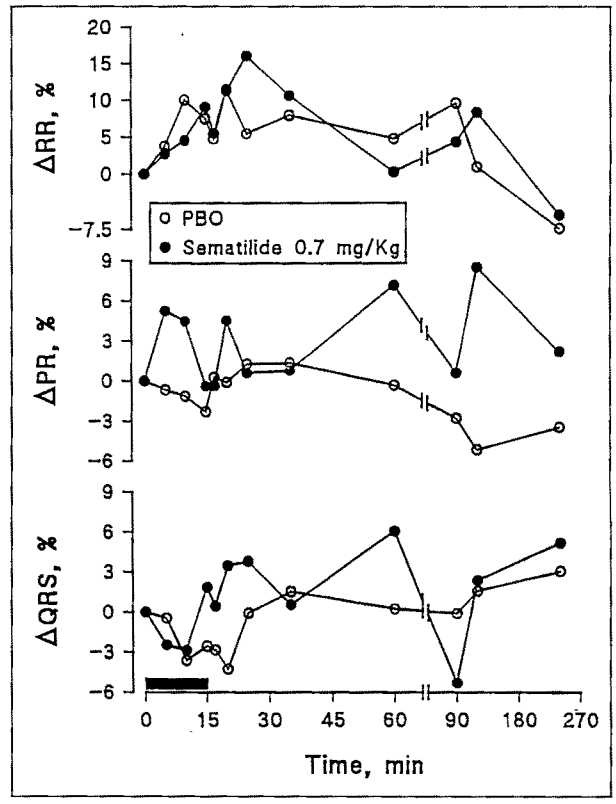


FIGURE 6. Changes in PR, QRS and RR as function of time during and after placebo (PBO) and sematilide (0.7 mg/kg). *Axes* as in Figure 5.

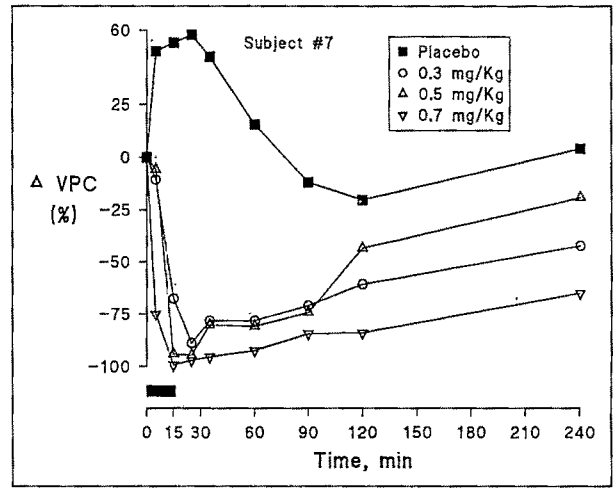


FIGURE 7. Relation between change in ventricular premature complex (Δ VPC) frequency and time after beginning of 15-minute infusion *(black bar)* during infusions of placebo and 0.3, 0.5 and 0.7 mg/kg of sematilide in 1 patient.

100% increase in the frequency of monomorphic ventricular ectopic beats. In a second subject infusion of 0.7 mg/kg was associated with a similar increase in the frequency of polymorphic ventricular beats, whereas infusion of 1.0 mg/kg was associated with marked QT prolongation and self-limited (up to 5 beats) runs of polymorphic ventricular tachycardia; no further infusions were administered in this subject. In the third patient, torsades de pointes needing cardioversion developed after 0.7 mg/kg (Figure 8). In this patient, the initial rhythm was ventricular bigeminy, with a QT interval of 400 ms. By the end of the infusion, the QT had lengthened to 600 ms, and intermittent junctional rhythm was present. Half an hour after the end of the infusion, a

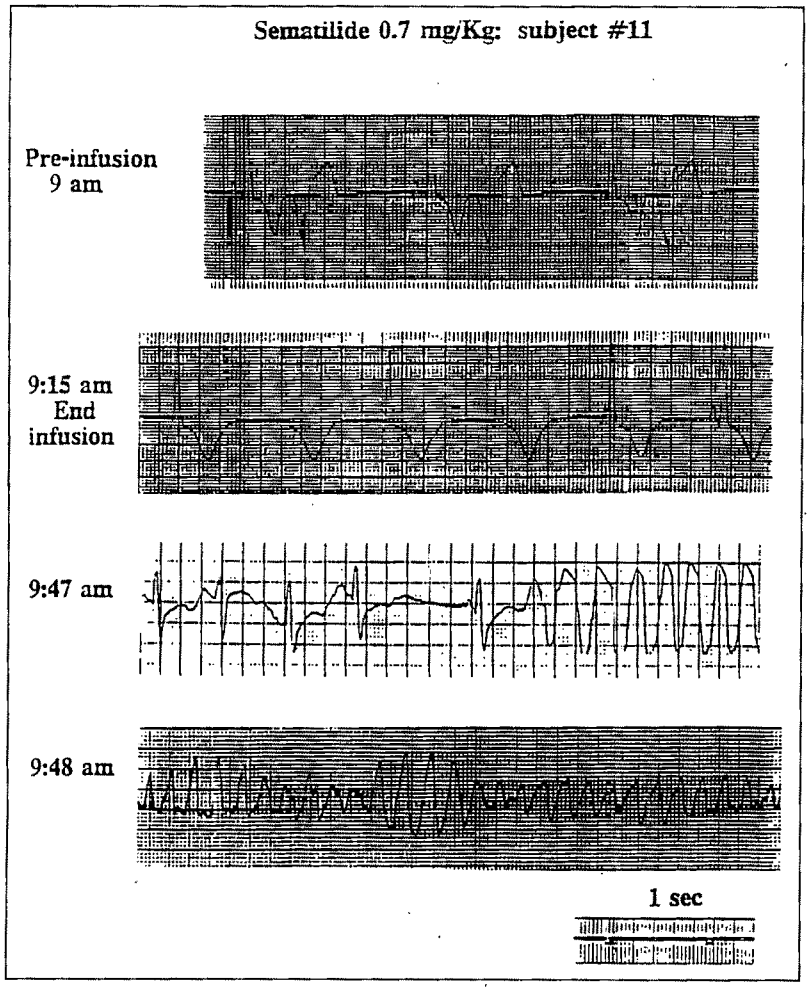


FIGURE 8. Torsades de pointes in a patient receiving 0.7 mg/kg of sematilide.

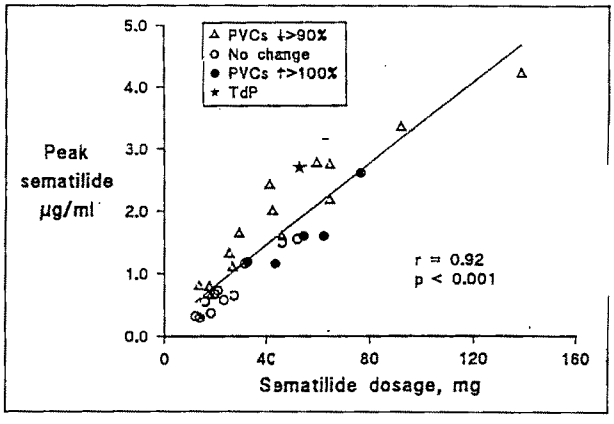


FIGURE 9. Relation between sematilide dose and peak plasma sematilide concentration. Symbols illustrate arrhythmia responses to sematilide during these infusions. PVCs = premature ventricular complexes; TdP = torsades de pointes.

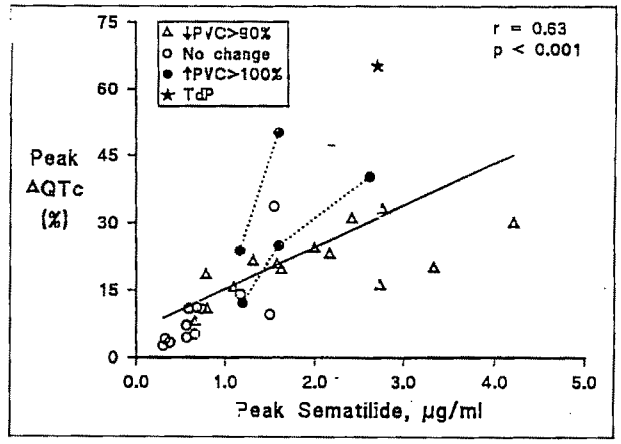


FIGURE 10. Relation between peak plasma sematilide and peak change in rate-corrected QT (ΔQTc). Symbols are identical to those in Figure 7. Abbreviations as in Figure 9.

long cycle was followed by a sinus beat and polymorphic tachycardia. Two direct-current shocks were required to restore normal rhythm, and the patient recovered without sequelae or further treatment.

The relation between dose and peak concentration was linear (Figure 9); arrhythmogenic responses were not observed at unusually high concentrations. Overall, there was also a good correlation between peak plasma concentration of sematilide and peak change in QTc (Figure 10). However, infusions during which an arrhythmogenic response was seen were associated with exaggerated QTc changes. There was a weak correlation ($r = 0.42$; $p < 0.02$) between peak plasma sematilide and maximum increase in RR interval; at high plasma sematilide concentrations (>2 μg/ml), heart rate decreased by 22 ± 14% ($p < 0.05$ vs baseline).

Two patients complained of headache during sematilide infusion. One patient developed transient hypotension (systolic pressure decreasing from 110 to 90 mm Hg) with infusion of 0.2 mg/kg, but no change in blood pressure was observed in the same patient during infusion of 0.3 mg/kg. There was no significant change in hepatic, renal or hematologic function on day 5 compared with that at baseline.

DISCUSSION

The aim of this study was to begin to define the pharmacology of sematilide in patients with arrhythmias. Sematilide exerted class III actions and prolonged QT interval without substantially altering PR or QRS. Interestingly, the drug also slightly decreased heart rate. This effect was also observed with other agents with class III properties such as amiodarone and sotalol, but these agents have ancillary properties (β blockade) that can also decrease heart rate, whereas sematilide does not block β receptors in vitro. The mechanism of this heart rate reduction is not known, but the finding is consistent with recent observations of Funck-Brentano et al[22] who found heart rate reduction with the d-isomer of sotalol, which is not thought to produce β blockade. They speculated that class III drugs may produce marked action potential prolongation in the sinus node, thereby decreasing heart rate. Such heart rate reduction is a recognized risk factor for the development of torsades de pointes.[13,14]

As with sotalol and NAPA, and unlike quinidine, the increase in QT interval produced by sematilide was dose- and concentration-related. As shown in Figure 10, a 25% increase in QT interval was associated with peak plasma sematilide concentration of approximately 2.0 μg/ml, and the 2 serious arrhythmogenic responses occurred in association with peak plasma sematilide concentrations of 1.6 (nonsustained) and 2.7 μg/ml (torsades de pointes). We recently reported that like other drugs associated with torsades de pointes,[11,23] sematilide can produce early afterdepolarizations and triggered activity in canine cardiac Purkinje fibers driven slowly in low extracellular potassium (2.7 mmol).[24] This finding and the occurrence of torsades de pointes in this study reinforce the link between in vitro and in vivo rhythm abnormalities. Thus, we believe that early afterdepolarizations and triggered activity should be specifically sought during the preclinical evaluation of a new antiarrhythmic entity as potential clues to a risk for torsades de pointes during clinical trials.

Sematilide transiently suppressed these nonsustained ventricular arrhythmias in 5 of 14 subjects. As shown in Figure 10, these responses occurred at plasma concentrations >0.8 μg/ml, whereas infusions during which no change in arrhythmia frequency was seen were all associated with peak plasma concentrations <1.55 μg/ml. Because this was a dose-ranging design, the frequency with which sematilide suppressed VPCs was necessarily underestimated. However, the range of plasma concentrations associated with suppression of nonsustained ventricular arrhythmias was also that in which arrhythmogenic responses were seen. The mechanisms underlying isolated VPCs and episodes of nonsustained ventricular arrhythmias are unknown. Some studies suggested reentry as a possible mechanism,[25,26] but agents that are most effective against these nonsustained ventricular arrhythmias (class Ic drugs) have limited efficacy in sustained reentrant ventricular arrhythmias. Thus, alternate mechanisms may be possible in some or all patients. For example VPCs, such as those shown in the top panel of Figure 7, may actually represent triggered activity related to early afterdepolarizations, which was then exacerbated by sematilide. Obviously, knowledge of such a mechanism may be helpful in avoiding QT-prolonging drugs in such patients. In this study, baseline QT intervals were not predictive of subsequent response to sematilide.

We demonstrated that sematilide exerts class III activity in patients. The absence of marked VPC suppression is consistent with animal and clinical data for other class III agents. Similarly, the development of marked QT prolongation and torsades de pointes represents a readily predictable extension of the drug's in vitro electrophysiology. The patients for whom drugs with class III actions may be desirable include those with sustained ventricular tachycardia, and ventricular and atrial fibrillation. Our study provides evidence that sematilide produces electrophysiologic effects in human subjects, that QT prolongs in a generally dose- and concentration-related fashion and that torsades de pointes can occur. Further studies in other patient cohorts are needed to define further the risks and benefits of the class III drug strategy.

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Epidemiologic Aspects of Isolated Systolic Hypertension and Implications for Future Research

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Isolated systolic hypertension represents an important public health issue in the 1990s because of its prevalence in the elderly and its importance as a risk factor for cardiovascular morbidity and mortality. Methodologic differences may account for the wide variation between prevalence rates in studies reported. With the advent of newer methods of blood pressure (BP) assessment, such as noninvasive ambulatory BP monitoring, it may be possible to define more accurately the true population at risk. Recent data from the Systolic Hypertension in the Elderly Program has indicated a clear benefit of treatment with a reduction in total stroke of 36%, and a reduction of 25 and 32% in the combined end points of coronary heart disease and cardiovascular disease, respectively. Further studies are now required to elucidate what treatment regimens are most effective in preferentially reducing both systolic BP, without producing undesirable effects such as diastolic hypotension, and fatal and nonfatal events. One such trial is underway in Europe using a drug regimen different from that in the Systolic Hypertension in the Elderly Program. The cost implications associated with treating the population at risk are potentially large but these are now based on firm scientific evidence.

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During recent years there has been increasing interest in isolated systolic hypertension, both as an independent risk factor for cardiovascular disease and as a clinical entity requiring treatment in its own right.[1-3] This heightened interest represents a significant change in attitude among physicians, since the level of diastolic blood pressure (BP) traditionally has been regarded as the key determinant of later target organ damage and hence, the major predictor of cardiovascular risk. It has also been used as the index against which the success of treatment regimens is measured. This approach has tended to obscure the contribution of other BP indexes and, in particular, systolic BP, to the point that any increase observed was often dismissed as a reflection of the natural process of aging, and was thought to bear little or no clinical significance in its own right. However, there is now an increasing pool of epidemiologic data drawn from both prospective and retrospective studies, which show the importance of systolic BP as a risk factor in its own right for cardiovascular morbidity and mortality.[4-6]

From a public health viewpoint, the importance of isolated systolic hypertension stems not only from its strength as a risk factor, but also from its relatively high prevalence in persons aged ≥65 years. The number of people within this age group is growing steadily in most Western societies. Despite this it was not until very recently that treatment was shown to be effective in reducing risk. However, the question of which antihypertensive agents are most effective for treatment of this condition remains unclear.

The definition of what constitutes isolated systolic hypertension still remains controversial and is largely arbitrary. The criteria generally used, although not representing any sort of biologic threshold, is a systolic BP >160 mm Hg with a diastolic BP <90 mm Hg. There remains debate about how many BP measurements are required to make the diagnosis and whether the cutoff level for diastolic BP should be 90 or 95 mm Hg. With the advent of newer methods of BP measurement, such as noninvasive ambulatory BP monitoring, some doubt has been cast on the meaning of such a definition. In many patients with isolated systolic hypertension (based on casual readings), ambulatory BP profile is "normal" for 58% of the daytime period.[7]

In this article, we review the previously accepted epidemiologic evidence regarding isolated systolic hypertension, and examine current and future directions for research in the area. In particular we have focused on the methodologic issues that may account for differences in prevalence rates and risk levels associated with isolated systolic hypertension.

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Blood pressure changes with aging: Observational changes in Western populations have shown an increase in systolic and diastolic BP until at least the sixth decade. Systolic pressure continues to increase almost linearly with advancing age (≥ age 60 years).[8] However, diastolic BP plateaus or even declines.[9] This may result from "exhaustion of susceptibles,"[10] in which persons with a higher BP may have an increased mortality at an earlier age and are therefore underrepresented.

The increase in systolic and diastolic BP with age has been seen in all Western societies studied. However, it is not observed among some of the isolated "unacculturated" hunter-gatherer populations,[11] such as the Melanesian Gaus of Fiji, natives of New Guinea, the Solomon Islands and the Brazilian Indians, who collectively tend to be lean and physically active, with possibly a lower sodium intake in their lifetime.[6] In these groups, both systolic and diastolic BP tends to remain constant throughout life or even decrease slightly with age. This suggests that environmental, rather than genetic, factors may contribute more to the subsequent determination of BP. This theory has been supported by the extensive studies examining the link between salt intake and BP levels.[12,13] The role of other nutrients and stress levels[14] have also been investigated, but none alone appear to explain these differences adequately.

Prevalence of isolated systolic hypertension: Most studies that have examined the prevalence of hypertension in Western society have focused on middle-aged populations, and have included enough older persons to enable an estimate of the prevalence of isolated systolic hypertension to be performed in the United States (Table I). Interpretation of these results has been confounded by a number of factors that might explain some of the variability in observed prevalence rates. These include differences in the method of BP measurement, criteria used to define systolic and diastolic cutoff levels, treatment status, and the age and sex distributions of the populations studied.

In the United States Health & Examination Surveys of 1960–1962[15] and 1971–1974,[16] prevalence rates for isolated systolic hypertension, based on BP determination at a single visit, was approximately 16% among persons aged >60 years (15% for men and 25% for women). In persons <60 years, the prevalence rate was <2%.

A recent meta-analysis, in which a second order regression model was used to describe the relation between isolated systolic hypertension prevalence and age in the various major studies, produced a prevalence of 0.8% at 50 years of age, 5.0% at 60, 12.6% at 70 and 23.6% at 80 years.[17] The prevalence was higher in women than in men, and higher in black than in white persons of the same age and sex. A high prevalence rate was also observed in persons already taking antihypertensive medication. This may reflect a more effective reduction in the diastolic component in response to treatment.

Altering the cutoff levels used to define isolated systolic hypertension can also have a substantial effect on prevalence rates. For example, in the U.S. Hypertension Detection and Follow-up Program population, the prevalence of isolated systolic hypertension in the 60 to 69 year age stratum was 5.6% when a diastolic BP cutoff at 95 mm Hg was used (systolic BP >160 mm Hg). However, this increased to 8.1% when the diastolic cutoff was reduced to 90 mm Hg. Conversely, reducing systolic BP to 140 mm Hg and keeping diastolic BP fixed results in an increased prevalence of 22.8%.[18]

One of the most significant factors affecting the prevalence of isolated systolic hypertension is the number of occasions on which BP is measured. Most studies have determined prevalence on the basis of a single BP measurement, but this may lead to a considerable overestimate. In his study of an elderly retirement community at Seal Beach, California, Colandrea et al[19] showed that with repeated measurements, the prevalence rates for isolated systolic hypertension decreased from 14.9% in men and 12.3% in women to 2.1 and 3.1% respectively. This decrease partly reflects both acclimatization to measurement and regression to the mean. It was also partly explained by an increase in diastolic BP in 14% of subjects, and a decrease in systolic together with an increase in diastolic BP in a further 6%.[10]

One method for overcoming transient elevations in BP that occur during clinic measurement is to use 24-hour ambulatory BP. This technique allows BP to be measured automatically using a noninvasive method at frequent predetermined intervals (e.g., half hourly) throughout the day and night. It has been shown to have good reproducibility and is subject to little, if any, "white-coat" or placebo effect. Ambulatory monitoring also provides BP measurements within a subject's normal environment.

Studies using this technique have demonstrated that many patients with sustained isolated systolic hypertension in a clinic setting have a substantially lower mean ambulatory BP during the daytime recording so that their ambulatory BP is in fact normal for a substantial proportion of the time.[7]

Until large-scale prospective studies examining the relation between ambulatory BP profile and development of subsequent cardiovascular morbidity and mortality are completed, the available estimates of prevalence and risk must be derived from studies using casual BP readings measured on a single occasion. On this basis in the United States, the population currently at risk with isolated systolic hypertension is probably in excess of 3 million persons.

Determinants of isolated systolic hypertension: Data from the Framingham study has been examined to determine whether the development of isolated systolic hypertension can be predicted from characteristics evident early in life. In this analysis, age, sex, systolic and diastolic BP, pulse pressure, mean arterial BP, Metropolitan relative weight, serum cholesterol level, serum uric acid level, cigarette smoking, heart rate, glucose intolerance and hematocrit were related to the development of isolated systolic hypertension over a 24-year period of follow-up. The results showed that a high systol-

TABLE I Prevalence Rates of Isolated Systolic Hypertension

Study	Year	Study Type	Source Population (sampling frame)	Method of BP Determination	Race	Age	BP (mm Hg)	Prevalence Rates of ISH*	
								Men	Women
Framingham[33]	1948–1978	Longitudinal	Community of Framingham, MA (entire adult community aged 30–62 years free of coronary heart disease at initial examination)	3 BP readings, left arm (first by nurse; 2nd & 3rd by physician later during clinic visit)	Both	>65 >75	SBP ≥160 DBP <90	14 25	23 30
Leisure World, California[19]	1965	Cross-sectional	Elderly retirement community (40% sample)	1 BP determination on each of 3 separate clinic visits	White	69.7 68.3	SBP ≥160 DBP <90	14.9 2.1	12.3 3.1
US National Health Examination Survey[15]	1960–1962	Cross-sectional	Adult population (US) (census tracts/housing units)	Average of 3 BP readings at examination center	Black White	65–74	SBP >160 DBP <90	25.5 15.0	38.9 30.7
Evans County, Georgia[34]	1967–1969	Cross-sectional	Survival cohort of the Evans County 1960–62 survey that included all persons aged ≥40 years and 50% of those aged 15–39	3 BP readings at 1 clinic visit; 2nd reading 30–60 min. later; 3rd reading 15 min. after 2nd reading	Black White	70–79	SBP >160 DBP <90	24.5 11.4	31.8 24.4
US National Health & Nutrition Survey I[25]	1971–1974	Cross-sectional	Population survey (US) (census tracts/housing clusters)	1 BP reading at examination center	Both	65–74	SBP ≥160 DBP <90	4.6	13.1
Hypertension Detection and Follow-up Program[18,35]	1972–1973	Cross-sectional	14 communities (US) (census tracts/housing developments)	3 sitting BP measurements, right arm; BP–mean of 2nd and 3rd reading	Black White	60–69	SBP ≥160 DBP <90	6.42 5.33	8.35 7.36
Rancho Bernado, California[23]	1972–1974	Cross-sectional	Community near San Diego, CA (entire adult community)	1 sitting BP measurement after 5 min. rest	White	60+	SBP ≥160 DBP <90	combined rates only 6.3	
Georgia[37]	1981	Cross-sectional	Adult population of Georgia (stratified probability clusters of housing units)	3 sitting BP measurements; BP–mean of 2nd & 3rd readings	Black White	70–79	SBP ≥160 DBP <90	9.7 0.8	30.3 9.3

*Rates expressed as percentages (i.e., per 100 persons).
BP = blood pressure; DBP = diastolic blood pressure; ISH = isolated systolic hypertension; SBP = systolic blood pressure.

TABLE II Mortality Ratios for Elevated Systolic Blood Pressure Compared with Normotensive Subjects—Data from Prospective Studies

Study	Follow-Up (yrs)	No. of Subjects	Definitions: ISH BP (mm Hg)	Definitions: Normotensive BP (mm Hg)	Mortality Ratios: All Cause	Mortality Ratios: Total Cardiovasc.	Mortality Ratios: Stroke	Mortality Ratios: Myocardial Infarct
Multiple Risk Factor Intervention Trial[22]	6	317,871	>160 / 75–79	110–119 / 75–79	2.6	NC	NC	NC
			>160 / 80–84	110–119 / 80–84	2.4	NC	NC	NC
Hypertension Detection and Follow-Up Program[35]	8	2,376	>160 / <90	<160 / <90	2.3	NC	NC	NC
Rancho Bernado[26]	6.4	2,636	>160 / <90	<160 / <90	1.5	1.3	2.2	0.6*
Leisure World[19]	6	3,245	>160 / <90	<160 / <90	1.6	6.9	3.0	2.2
Chicago Stroke Study[24]	3	2,772	>180 / <95	<180 / <95	1.6	2.0	2.5	1.7
Chicago Peoples Gas Company[25]	15	976	>140 / <90	<140 / <90	1.7	1.9	NC	2.0
Framingham Study[23]	30	2,470	>160 / <95	<140 / <95	1.9†	2.1†	NC	NC
					1.9‡	3.1†	NC	NC
Dutch Civil Servants[36]	15	2,063	>160 / <90	<135 / <90	2.4†	NC	NC	NC
					3.7‡			
	25		>160 / <90	<135 / <90	3.2†	NC	NC	NC
					1.7‡			

*Among patients not taking medication.
†Men.
‡Women.
BP = blood pressure; Cardiovasc. = cardiovascular mortality; ISH = isolated systolic hypertension; NC = not calculated.

ic BP and a high pulse pressure were predictive of developing isolated systolic hypertension, as was excessive weight, in women.[10]

Isolated systolic hypertension as a risk factor: Epidemiologic evidence has linked an increase in systolic BP with an increasing risk of coronary artery disease, stroke and all-cause mortality. The first convincing demonstration of this association was provided by the Build and Blood Pressure Study which, in 1959, reported the pooled experiences of policy holders from 26 American and Canadian insurance companies. Three million nine hundred thousand policy holders who had been issued with ordinary life insurance contracts between 1935 and 1953 were traced to the policy anniversaries in 1954.[20]

The study demonstrated an increase in all-cause mortality with successive increments of systolic BP at any given level of diastolic BP. This effect was observed across the entire age range (15 to 69 years) that was studied. However, information was only available for systolic BP <167 mm Hg, since the data above this level were insufficient to yield statistically valid conclusions.[20]

The findings of the 1959 study were confirmed by a subsequent analysis of life insurance policy holders published in 1979. This study reported that persons with isolated systolic hypertension had an all-cause mortality 51% higher than that in normotensive persons.[21]

Similar increases in all-cause mortality have been observed in various prospective studies (Table II). For example, in the U.S. Hypertension Detection and Follow-up Program, the all-cause mortality rate (after adjustment for age, race and sex) was 17.6% in those with isolated systolic hypertension (systolic BP ≥160 mm Hg, diastolic BP <90 mm Hg) and 7.5% in normotensive persons. Multiple logistic regression demonstrated an approximate 1% increase in mortality for each millimeter increase in systolic BP.[18]

Another large prospective study involved the 6-year follow-up of the 360,000 men aged 35 to 57 years who had been screened for inclusion into the Multiple Risk Factor Intervention Trial. The prevalence of systolic hypertension among these subjects was <1%. At any given level of diastolic BP, increasing levels of systolic BP were associated with an increase in the age-adjusted all-cause mortality rate.[22] Multivariate analysis of data from men with a diastolic BP of 75 to 79 mm Hg showed a 2.6-fold higher mortality among those with systolic BP >160 mm Hg than the mortality in those who had a systolic BP of 110 to 119 mm Hg. In those with a diastolic BP between 80 and 84 mm Hg, the mortality ratio between the 2 groups was 2.4.

Data from the Framingham study have linked isolated systolic hypertension to an increased risk of cardiovascular mortality as well as an increased risk of nonfatal stroke and myocardial infarction.[4,8,23] This study has involved a cohort of 5,209 men and women followed biennially since 1948 (approximately 85% of the original cohort have complied with follow-up). After 24 years of follow-up, the age-adjusted odds ratio for death from cardiovascular disease among those with isolated systolic hypertension compared with cohort members who had a BP consistently <140/95 mm Hg was 2.1 for men and 3.1 for women.[23]

TABLE III Incidence of Fatal Events Reported in Patients Aged ≥ 60 Years in Randomized Controlled Trials—Summary of Meta-Analysis*

Study	Total Mortality	Cardiovascular Mortality	Cerebrovascular Mortality	Cardiac Mortality	Ischemic Heart Disease
Kuramoto	+7 (−59 to +180)	+7 (−77 to +402)	+113 NC	NR	−47 NC
European Working Party on Hypertension in the Elderly	−9 (−28 to +15)	−27† (−46 to −1)	−32 (−61 to +119)	−38† (−61 to −1)	−60† (−80 to −4)
Coope/Warrander	−3 (−30 to +42)	−22 (−49 to +20)	−70† (−89 to −16)	+1 (−38 to +63)	0 (−42 to +70)
Hypertension Detection Follow-up Program	−16 (−32 to +2)	NR	NR	NR	NR
Australian Therapeutic Trial Mild Hypertension	−23 NC	−61 (−92 to +102)	−1 NC	NR	−75 (−97 to +119)
Total	−14 (−26 to +1)	−28† (−45 to −6)	−41† (−63 to −5)	−24 (−46 to +8)	−28 (−54 to +12)

*Percent difference between active treatment and control groups.
†$p < 0.05$ (all other results are not significant).
NC = not calculated; NR = not reported.
Adapted from: Staessen J, Van Hoof R, Fagard R, Amery A. Epidemiology of treated and untreated hypertension in the elderly. In: Amery A, Staessen J, eds. Handbook of Hypertension. vol 12. Hypertension in the Elderly. Elsevier Science, 1989: 320–351.

These findings are similar to others[24-26] (see Table II) that have reported up to a threefold increase in stroke and up to a 2.2-fold increase in myocardial infarction among those with isolated systolic hypertension. Together these findings strongly suggest that an increase in systolic BP represents a significant predictor of future vascular events.

Hypertension as a risk factor in the very elderly: The only group of subjects for whom the predictive value of an elevated systolic (or diastolic) BP remains unclear is the very elderly. Recent studies both in Finland and Sweden have suggested that in this age group, increased BP may actually confer an advantage in terms of increased survival.[27,28] For example, in the Finnish study, in which all subjects were aged ≥85 years, survival increased as diastolic BP increased.[27] A possible confounder that may help explain this finding is the presence of preexisting heart disease in some subjects, which may be associated with a reduced BP.

Value of treatment: Before publication of the results of the Systolic Hypertension in the Elderly Program in June 1991,[29] there was a lack of evidence demonstrating a reversal of risk from treatment with isolated systolic hypertension. Up to that time the larger morbidity/mortality trials of antihypertensive treatment had used diastolic BP levels as the principal entry criteria. A recent meta-analysis of trials confined to the elderly,[30] or which included sufficient numbers of elderly persons to enable a subgroup analysis, demonstrated a statistically significant reduction in cerebrovascular (but not cardiac) mortality among those receiving active treatment (Table III).

The exception to this result was the European Working Party on Hypertension in the Elderly study, in which a significant reduction in cardiac mortality was observed in the actively treated group.[31] In this latter study, the beneficial effect of treatment did not extend to persons >80 years of age, although the numbers in this subgroup were small. This result has left the question of whether to treat the very elderly in doubt.

In 1984, after a successful pilot study, the National Heart, Lung, and Blood Institute commenced recruitment for a trial to determine whether antihypertensive drug treatment was effective in reducing the risk of stroke (fatal plus nonfatal) in a cohort of men and women aged ≥60 years with isolated systolic hypertension.[29] Four thousand seven hundred and thirty-six persons (43% men, 14% black) were recruited over a 3-year period and randomized to receive either a stepped antihypertensive regimen or matching placebo. At randomization, the mean age was 72 years, the average BP was 170 mm Hg systolic/77 mm Hg diastolic, and most of the subjects (>90%) had not had previous episodes of cardiovascular disease.

Subjects randomized to active treatment initially received chlorthalidone (12.5 mg/day) with the aim of reducing systolic BP to <160 mm Hg (in those whose systolic BP was initially >180 mm Hg) and to produce a 20 mm Hg decrease in systolic BP in the remaining subjects. In those who were unable to achieve BP goal, treatment was increased initially to chlorthalidone 25 mg and subsequently with the addition of atenolol (25 or 50 mg/day); for those unable to tolerate atenolol, reserpine was given.[29]

During an average follow-up period of 4.5 years, systolic BP was (on average) 11 to 14 mm Hg lower and diastolic BP was 3 to 4 mm Hg lower in the actively treated group. During this time, about 10% of the "actively treated" group discontinued active treatment, whereas the percent of those receiving placebo treatment who required an introduction to active therapy increased progressively from 13% at year 1 to 44% at year 5.[29] BP in almost 50% of the actively treated participants was controlled with chlorthalidone alone.

The most impressive finding in the study was a 36% reduction in the incidence of stroke ($p = 0.0003$), which

represented an absolute benefit of 6 events per 1,000 patient years of treatment. The incidence of nonfatal myocardial infarction was 27% lower and the all-cause mortality 13% lower in the treated group. An increase in nonvascular mortality was observed in those treated, but this was small and not statistically significant (109 vs 103 deaths in the placebo group).

Because of the relatively mild degree of systolic hypertension present in this population (84% had a systolic BP <180 mm Hg) and the relatively large number of treatment crossovers, this result is impressive and leaves no doubt about the value of treatment. However, active treatment produced a variety of symptoms and abnormal laboratory findings more often than placebo therapy. For example, problems specified as intolerable were reported by 38% of those taking active treatment but by only 21% of those receiving placebo. It will continue to be necessary to balance the benefit to be gained by treatment against the offsetting influences of adverse effects of medication when deciding whether treatment is worthwhile in any particular subject.

Because all of the currently available antihypertensive drugs can effectively reduce systolic BP, the question now turns to which of the available agents is most useful for this condition.[32] Another large placebo-controlled, double-blind trial is in progress in Europe.[17] This trial is using a different drug regimen (step 1, nitrendipine; step 2, enalapril; step 3, hydrochlorothiazide), and results are not expected until 1997. This will provide information about the efficacy of a very different drug regimen. Because additional placebo-controlled studies will be unethical, it is likely that decisions about optimal drug therapy will require assessment of indirect end points such as the relative effects of the drug on systolic and diastolic BP or their effects on atheroma assessed indirectly by carotid duplex scanning.

Because of the high prevalence of the condition in elderly persons and the increasing numbers of elderly in most Western communities, the likely costs of treatment are substantial. However, this cost must be set against the cost of caring for patients with stroke and other forms of cardiovascular disease, which is also substantial. Further research is also required, using techniques such as ambulatory BP monitoring, to identify persons with isolated systolic hypertension (based on casual clinic readings) who are at greatest risk of having a morbid or fatal event, and are therefore most likely to benefit from treatment.

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Morphologic, Hemodynamic and Coronary Perfusion Characteristics in Severe Left Ventricular Hypertrophy Secondary to Systemic Hypertension and Evidence for Nonatherosclerotic Myocardial Ischemia

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Patients with the clinical diagnosis of ischemic heart disease who were found to be free of significant coronary artery atherosclerotic disease (n = 150) underwent coronary vasodilator reserve testing, 2-dimensional echocardiography, and dipyridamole limited-stress thallium testing. After exclusions (predominantly for technically poor coronary artery Doppler signals or suboptimal echocardiography), 100 patients formed the study population. The purpose was to characterize typical cardiac and coronary artery findings in hypertensive patients with severe left ventricular (LV) hypertrophy (n = 15) and to investigate the evidence for myocardial ischemia unrelated to coronary atherosclerosis in early and advanced hypertensive heart disease. Normotensive and hypertensive control groups without LV hypertrophy (n = 12 and 34, respectively) were used for comparison. Severe LV hypertrophy was defined as LV mass index ≥50% above established gender specific norms using 2-dimensional-directed M-mode echocardiography and the cube equation corrected to agree with necropsy estimates of mass. Clinical characteristics more often associated with severe LV hypertrophy were black race (67%), diabetes mellitus (33%), proteinuria (47%) and elevated creatinine (1.5 ± 0.9 mg/dl). Baseline electrocardiograms and dipyridamole limited-stress thallium scans were highly likely to be abnormal (94 and 73%, respectively). Both eccentric and concentric cardiac hypertrophies were found in the severe group. Ejection fraction was significantly lower (0.51 vs 0.68, p = 0.002) and basal coronary flow velocity higher (12.0 vs 5.0 cm/s, p = 0.0004) among these patients when compared with normotensive control patients. Coronary flow reserve did not differ between control groups but was significantly depressed in patients with severe LV hypertrophy (2.5 vs 3.9, p = 0.001). This, together with the prevalent evidence of resting and stress-induced ischemia, strongly supports the concept of myocardial ischemia unrelated to coronary atherosclerosis in this group.

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Hypertensive left ventricular (LV) hypertrophy is classically defined by electrocardiographic, echocardiographic and autopsy-determined LV mass criteria.[1–5] A body of data now exists to support the speculation that LV hypertrophy, though initially an adaptive mechanism to decrease wall stress, may culminate with adverse clinical events, including early death, congestive heart failure, chronic myocardial ischemia and fibrosis, and ventricular arrhythmias.[6–9] This study investigates cardiac morphology and hemodynamic and coronary perfusion characteristics found in patients free of significant epicardial coronary artery atherosclerotic disease who have severe hypertensive LV hypertrophy as defined by echocardiography and established gender-specific mass criteria.[4] These findings are then contrasted with those found in a normal nonhypertensive group and in a group with hypertension but normal LV mass, a group considered to represent early hypertensive heart disease.[10,11] Correlation of these parameters with noninvasive markers for ischemia was investigated in order to establish the evidence for myocardial ischemia unrelated to coronary atherosclerosis in early and advanced hypertensive heart disease.

METHODS

Patients: Over a period of 3½ years, 150 patients who underwent cardiac catheterization because of a suspicion of coronary atherosclerosis were found to have no or insignificant disease and were enrolled in a protocol whose purpose was to obtain both invasive and noninvasive data for investigation of nonatherosclerotic ischemic heart disease (see Figure 1). Insignificant disease was defined as ≤30% luminal diameter narrowing in a major coronary vessel or a major branch. However, 82% of study patients had normal coronary arteries. The other 18% had minor luminal irregularities or up to 30% luminal diameter narrowing. Coronary flow reserve was not significantly different between these. Patients with valvular or congenital heart disease and primary myo-

pathic disease were excluded. Further testing included invasive measurement of coronary vasodilator reserve using the intracoronary Doppler catheter and intravenous dipyridamole, dipyridamole limited-stress thallium-201 perfusion scans, and 2-dimensional echocardiography. All studies were approved by the Human Assurance Committee of the Institutional Review Board at the Medical College of Georgia. Results of the initial 68 patients in this series (48 after exclusions) were presented in a study by Houghton et al.[12] The purpose of this earlier work was to investigate the relation between thallium defects and abnormalities in coronary flow reserve in hypertensive patients. The same methodology was used throughout the larger study.

Of the 150 enrolled patients, 123 (82%) had acceptable signals of phasic coronary blood flow velocity at baseline and after hyperemic doses of intravenous dipyridamole. After review, 13 patients were found to have previously unrecognized exclusions. Ninety-five of the remaining patients had hypertension, defined as repeated blood pressure measurements >140/90 mm Hg or self-reported taking of antihypertensive medication. Echocardiography was adequate for calculation of LV mass in 88. Of these, 15 (17%) had severely increased LV mass index defined by ≥50% above gender-specific upper normal limits established by the Framingham Heart Study.[4] This was designated as severe hypertensive LV hypertrophy. Thirty-four patients (39%) had hypertension but normal LV mass index; this was referred to as the hypertensive control group. Fifteen patients were normotensive; 12 of these had adequate echocardiograms and were used as normal control subjects. The 2 control groups were used for comparison of findings in the group with severe LV hypertrophy. Finally, 39 hypertensive patients had increased LV mass index but <50% above gender-specific upper normal limits. This last group, referred to as mild to moderate LV hypertrophy, is mentioned for completeness and is not the subject of the current study.

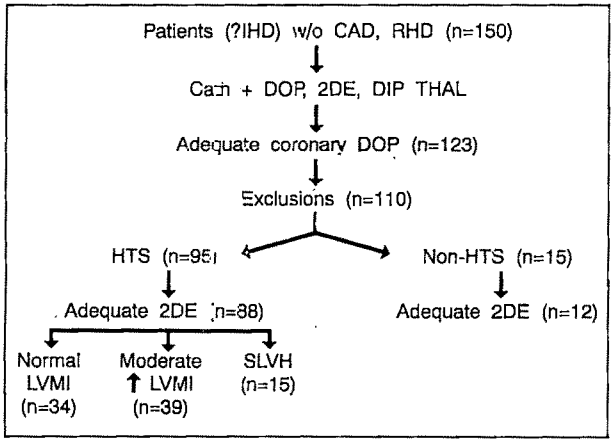


FIGURE 1. Diagram depicting study schema in which 150 patients without coronary artery disease (CAD) or rheumatic heart disease (RHD) were recruited for investigation of nonatherosclerotic ischemic heart disease (IHD). CATH = cardiac catheterization; 2DE = 2-dimensional echocardiography; DIP THAL = dipyridamole stress thallium testing; DOP = Doppler catheter coronary flow velocity recordings; HTS = hypertensive; LVMI = indexed left ventricular mass; SLVH = severe left ventricular hypertrophy; w/o = without.

Coronary vasodilator reserve testing: After infusing 10,000 U of heparin, the intracoronary Doppler catheter was placed through a giant lumen guiding catheter over a 0.014-inch guidewire placed distally in the selected coronary artery. The Doppler catheter was then advanced into the proximal portion of the selected artery or the distal left main artery. Pulsed Doppler signals were range-gated into the proximal left anterior descending or circumflex artery. In each case, the Doppler catheter position and the range gate were adjusted to obtain an optimal audio signal and phasic flow velocity tracings. Coronary flow velocity was then measured at baseline and after administration of hyperemic doses of intravenous dipyridamole (0.6 to 0.85 mg/kg infused over 4 to 6 minutes). Coronary flow reserve was calculated as follows: CFR = FV2/FV1, where CFR = coronary flow reserve, FV2 = mean coronary flow velocity at peak hyperemia, and FV1 = mean coronary flow velocity at baseline.

Normal coronary flow reserve was defined as ≥3:1. This value was arrived at on the basis of reports from other laboratories and our own experience.[12–14] Impaired flow reserve was defined as a ratio <3:1. Indexed minimal coronary vascular resistance was calculated as follows:

$$\text{mCVR} = \frac{\text{hMAP}}{\text{FV2}} \div \frac{\text{bMAP}}{\text{FV1}}$$

where mCVR = minimal coronary vascular resistance indexed by basal resistance, hMAP = mean arterial pressure at peak hyperemia, and bMAP = mean arterial pressure at baseline.

Echocardiographic estimation of left ventricular hypertrophy: LV mass was calculated using the cube equation,[15] measurements obtained in accordance with the American Society of Echocardiography criteria[16] and a regression equation derived to agree with necropsy mass estimates.[17] The methodology is identical to that used in our earlier study and is detailed in Houghton et al.[12] LV mass was indexed by body surface area; gender-specific upper normal limits from the Framingham Heart Study were used as follows: normal <131 g/m^2 for men and <100 g/m^2 for women.[4] Relative wall thickness was calculated as 2 × posterior wall thickness ÷ LV internal dimension at end-diastole. Concentric LV hypertrophy was present when calculated LV mass index exceeded gender-specific norms and relative wall thickness was ≥0.45; similarly, eccentric LV hypertrophy was present when LV mass index was increased and relative wall thickness was <0.45.[18] When LV internal dimension at end-diastole indexed by body surface area exceeded 3.2 cm/m^2 for women and 3.1 cm/m^2 for men, the left ventricle was defined as dilated.[19]

Intravenous dipyridamole limited-stress thallium-201 scintigraphy: This procedure was performed in the fasting state within 3 months of cardiac catheterization. Antianginal therapy was routinely held for ≥12 hours before testing. Theophylline compounds were withheld for 48 hours before testing. The following protocol was approved by the Human Assurance Committee at the Medical College of Georgia: dipyridamole (0.4 mg/kg)

was infused intravenously over 4 minutes, followed by symptom-limited treadmill exercise using modified or standard Bruce protocols. Thallium-201 was injected at peak exercise which was continued for 30 to 60 seconds. Identical delayed images were acquired 3 to 4 hours later. Further details may be found in the study by Houghton et al.[12]

Statistical analysis: Summary data are expressed as mean ± 1 SD. Where appropriate, the unpaired *t* test, the chi-square test, analysis of variance and Fisher's exact test (2-tailed) were used to assess statistical significance, with $p < 0.05$ considered significant.

RESULTS

Patient characteristics: Clinical characteristics of the normal control group, the hypertensive control group, and the group with severe LV hypertrophy are summarized in Table I. Individual patient findings in the group with severe LV hypertrophy are summarized in Table II. The normal group was significantly younger and leaner than the group with severe hypertrophy. Although the normal group was predominantly caucasian (83%), the hypertensive control group was nearly evenly split between caucasian and black races. In contrast, the group with severe hypertrophy was largely black (67%) and the patients were more likely to have diabetes mellitus (33%) and proteinuria (47%). No patient in the normal control group had either disease. By way of comparison, although not the subject of this study, patients in the group with mild to moderate hypertrophy were also more frequently black (72%) and more likely to have diabetes mellitus (38%) and proteinuria (41%) than the control groups. In all 3 hypertensive control patients with proteinuria, the level was graded as trace (<20 mg/dl), whereas 5 of the 7 patients with proteinuria in the group with severe hypertrophy had 2- or 3-plus levels (100 to 300 mg/dl). Likewise, serum creatinine was significantly increased in the group with severe hypertrophy. Only 6 of 15 patients (40%) had a normal serum creatinine (<1.2 mg/dl). This is in comparison to 9 of 11 patients (82%) with normal measured values in the normal control group and to 29 of 34 patients (85%) in the hypertensive control group. In the group with mild to moderate hypertrophy, 67% had normal serum creatinine. Finally, all subjects in the normal group and all but 2 in the hypertensive control group had measurements <1.4 mg/dl. Hypertensive end-organ damage (defined as a history of stroke or congestive heart failure, ejection fraction <55%, creatinine ≥1.4 mg/dl, proteinuria > trace, or indexed LV internal dimension at end-diastole >3.1 cm/m^2) was present in 13 of 15 patients (87%) in the group with severe hypertrophy compared with 8 of 34 (24%) in the hypertensive control group. Both baseline electrocardiograms and dipyridamole limited-stress thallium scans were most likely to be abnormal in the group with severe hypertrophy (93.5 and 73%, respectively). Baseline electrocardiographic abnormalities were evenly split between LV hypertrophy ± ST-T-wave changes and isolated ST-T-wave changes. Thallium defects involved the circumflex alone in 4 patients, the circumflex plus another artery (left anterior descending or posterior descending) in 4 patients, the posterior descending artery alone in 1 patient, and the left anterior descending plus posterior descending artery in 2 patients. Nine patients had thallium defects with stress, and they underwent reperfusion at rest; the remaining two patients had fixed defects. In the group with mild to moderate hypertrophy, abnormal baseline electrocardiograms and stress thallium scans were found in 69 and 42%, respectively.

TABLE I Clinical Characteristics of 12 Control Nonhypertensive Patients, 34 Control Hypertensive Patients and 15 Hypertensive Patients with Severe Left Ventricular Hypertrophy but Without Significant Coronary Atherosclerosis

	Non-HTS Control Group	HTS Control Group	Severe HTS LV Hypertrophy
No. of pts.	12	34	15
Age (years)	44 ± 13*	52 ± 10	55 ± 11
Female gender	6 (50%)	19 (56%)	9 (60%)
Black/white	2/10*	16/18	10/5
Body mass index (kg/m^2)	25.2 ± 5.5*	30.0 ± 5.9	31.2 ± 8
Diabetes mellitus	0*	5 (15%)	5 (33%)
Proteinuria	0*	3 of 31 (10%)*	7 (47%)
Creatinine (mg/dl)	0.9 ± 0.2*	1.0 ± 0.2*	1.5 ± 0.9
Normal electrocardiogram	5 (42%)	16 (47%)*	1 (6.5%)
Thallium scan			
Positive	1 (10%)*	8 (30%)*	11 (73%)
Negative	9 (90%)*	19 (70%)*	4 (27%)

*$p < 0.05$ compared with severe LV hypertrophy group.
HTS = hypertensive; LV = left ventricular.

TABLE II Individual Clinical Characteristics of the Biggest Hearts (left ventricular mass index ≥ 50% above upper normal) in a Hypertensive Population Without Significant Coronary Atherosclerosis

Pt. No.	Age (yr)	Gender	Race	BMI (kg/m^2)	DM	Cr (mg/dl)	ECG	Thallium Scan
1	67	F	W	19.3	0	1.9	LVH+S	Normal
2	53	M	B	30.0	0	1.4	LVH+S	Abnormal
3	50	F	W	26.8	+	4.0	LVH+S	Abnormal
4	68	F	B	41.2	0	0.9	ST-T	Abnormal
5	68	F	B	27.1	+	1.2	LVH	Abnormal
6	49	M	W	29.3	0	1.0	ST-T	Abnormal
7	33	M	B	51.9	0	1.7	ST-T	Abnormal
8	63	M	B	27.2	0	2.2	ST-T	Abnormal
9	61	F	B	28.2	+	0.9	ST-T	Abnormal
10	50	M	W	36.2	0	1.2	NL	Abnormal
11	45	F	W	37.4	0	0.8	ST-T	Normal
12	63	F	B	29.6	+	2.4	LVH+S	Abnormal
13	60	M	B	34.7	0	0.9	LVH+S	Normal
14	40	F	B	23.4	0	1.6	LVH+S	Normal
15	59	F	B	25.6	+	0.7	ST-T	Abnormal

B = black race; BMI = body mass index; Cr = serum creatinine; DM = diabetes mellitus; ECG = electrocardiogram; LVH = left ventricular hypertrophy; S = strain pattern; ST-T = ST-segment and T-wave changes.

Morphologic, hemodynamic and coronary perfusion characteristics: Tables III and IV present morphologic, hemodynamic and coronary perfusion characteristics found in the 2 control groups and in the group with severe LV hypertrophy. Morphologic characteristics found in the severe group included development of LV wall hypertrophy ± dilatation together with left atrial enlargement. LV posterior wall thickness, indexed internal dimension at end-diastole and left atrial dimension were normal and not significantly different between

TABLE III Cardiac Morphology and Hemodynamic and Perfusion Characteristics in Control Groups and in Patients With Severe Hypertensive Left Ventricular Hypertrophy Without Significant Coronary Atherosclerosis

	Non-HTS Control Group	HTS Control Group	Severe HTS LV Hypertrophy
No. of pts.	12	34	15
LV mass index (g/m^2)	84 ± 16*	88 ± 16*	192 ± 36
Posterior wall thickness (cm)	1.0 ± 0.1*	1.0 ± 0.2*	1.5 ± 0.2
Indexed LV diastolic dimension (cm/m^2)	2.4 ± 0.2*	2.4 ± 0.3*	2.9 ± 0.35
Left atrial dimension (cm)	3.6 ± 0.5*	3.9 ± 0.6*	4.9 ± 0.7
Relative wall thickness	0.46 ± 0.1	0.45 ± 0.1*	0.53 ± 0.1
Ejection fraction	0.68 ± 0.1*	0.69 ± 0.1*	0.51 ± 0.1
Mean arterial pressure (mm Hg)	98 ± 11*	109 ± 15*	135 ± 29
LV end-diastolic pressure (mm Hg)	13.8 ± 4.4*	15.9 ± 7.2*	21.4 ± 8.4
Basal coronary flow velocity (cm/s)	5.0 ± 2.7*	8.1 ± 4.5*	12.0 ± 5.3
Hyperemic coronary flow velocity (cm/s)	19.0 ± 12.3	24.4 ± 10.3	27.9 ± 13.1
Coronary flow reserve	3.9 ± 0.9*	3.4 ± 1.2*	2.5 ± 1.0
Indexed minimal coronary resistance	0.25 ± 0.06*	0.3 ± 0.1*	0.41 ± 0.1

HTS = hypertensive; LV = left ventricular.
*p < 0.05 compared with severe LV hypertrophy group.

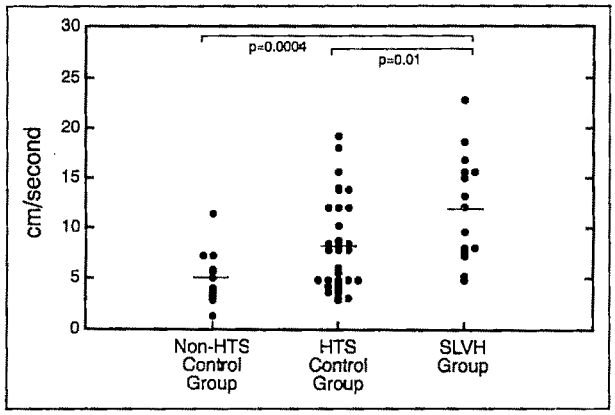


FIGURE 2. Basal coronary flow velocity in 12 nonhypertensive (HTS) control patients, 34 hypertensive control patients, and 15 hypertensive patients with severe left ventricular hypertrophy (SLVH).

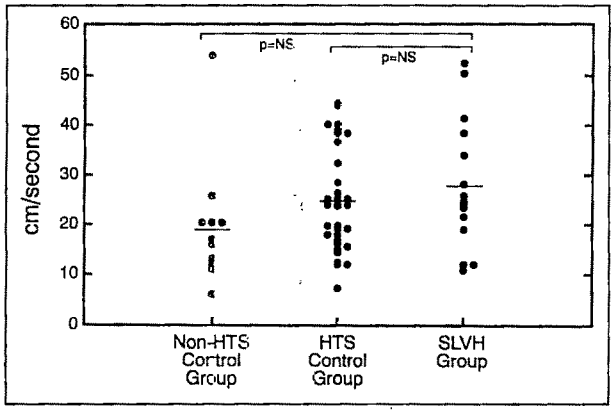


FIGURE 3. Hyperemic coronary flow velocity in 12 nonhypertensive (HTS) control patients, 34 hypertensive control patients, and 15 hypertensive patients with severe left ventricular hypertrophy (SLVH). NS = not significant.

control groups but were significantly increased in the group with severe hypertrophy (1.5 ± 0.2 cm, 2.9 ± 0.35 cm/m^2, and 4.9 ± 0.7 cm, respectively). Overall, relative wall thickness was significantly greater (0.53 ± 0.1, p = 0.03) and ejection fraction significantly lower (0.51 ± 0.1, p = 0.002) in patients with severe hypertrophy. However, 3 patients met criteria for eccentric dilated hypertrophy and 2 for eccentric hypertrophy alone. Both basal mean arterial pressure and LV end-diastolic pressure were significantly elevated in the severe hypertrophy group (135 ± 29 mm Hg, p = 0.0001 and 21 ± 8 mm Hg, p = 0.02). Both were recorded at baseline before coronary flow reserve testing. Of note was the progressive significant elevation in mean basal coronary flow velocity proceeding from the normotensive control to hypertensive control to severe LV hypertrophy group (5.0 ± 2.7 vs 8.1 ± 4.5 vs 12.0 ± 5.3 cm/s, Figure 2). Mean hyperemic coronary flow velocity was not significantly different between the 3 groups, although there was a similar increasing trend (Figure 3). Coronary flow reserve was not significantly different between control groups (3.9 ± 0.9 vs 3.4 ± 1.2), but it was significantly lower in the group with severe hypertrophy (2.5 ± 1.0, p = 0.001; Figure 4). Minimal coronary vascular resistance indexed for basal resistance was significantly increased in those with severe hypertrophy (0.41 ± 0.1, p = 0.004; Figure 5). Individual results of patients with severe hypertrophy are enumerated in Table IV. The fact that mean basal flow velocity in the proximal coronary arteries is usually elevated and may be as high as 23 cm/s but occasionally is in the normal range (4 to 8 cm/s) is of particular interest. This is probably related to varying levels of ventricular fibrosis.

DISCUSSION

This study demonstrates the characteristics found in severe hypertensive LV hypertrophy and compares them with normotensive and hypertensive control groups without hypertrophy. Because this study involves only patients free of significant coronary artery atherosclerosis and uses control groups without hypertrophy, it permits partial isolation and analysis of the effects of hypertensive LV hypertrophy; however, we realize that

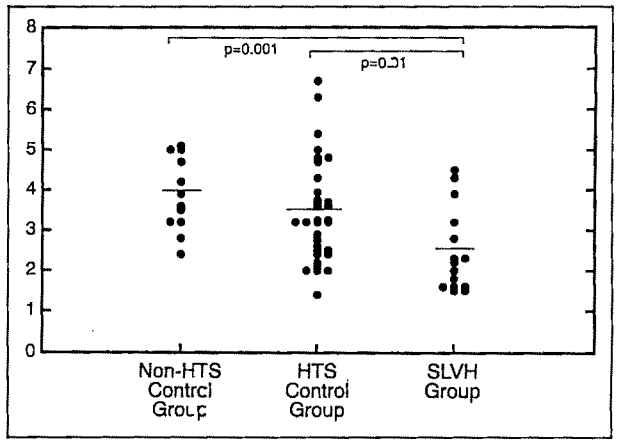


FIGURE 4. Coronary flow reserve in 12 nonhypertensive (HTS) control patients, 34 hypertensive control patients, and 15 hypertensive patients with severe left ventricular hypertrophy (SLVH).

TABLE IV Individual Morphologic, Hemodynamic and Coronary Perfusion Characteristics of the Biggest Hearts (left ventricular mass index ≥ 50% above upper normal) in a Hypertensive Population Without Significant Coronary Atherosclerosis

Pt. No.	LVMI (g/m^2)	MAP (mm Hg)	LA (cm)	PWT (cm)	LVIDI (cm/m^2)	RWT	EF	LVEDP (mm Hg)	FV1 (cm/s)	FV2 (cm/s)	CFR
1	185	154	5.3	1.5	2.4	0.71	0.53	40	12.1	19.0	1.6
2	236	75	3.5	1.8	2.5	0.67	0.77	10	15.0	23.4	1.5
3	156	115	4.1	1.4	2.8	0.55	0.78	25	13.2	21.6	1.6
4	179	132	5.0	1.5	2.6	0.56	0.58	24	8.0	38.4	4.5
5	151	148	4.5	1.3	3.0	0.48	0.53	29	8.0	12.0	1.5
6	222	113	5.0	1.4	3.4	0.42	0.4	15	16.8	34.0	2.0
7	233	116	6.1	1.6	2.6	0.44	0.6	10	22.8	50.4	2.2
8	199	168	5.4	1.7	2.5	0.67	0.32	21	15.6	25.8	1.8
9	160	121	4.5	1.1	3.2	0.36	0.66	11	4.8	10.8	2.3
10	200	147	4.0	1.4	2.9	0.41	0.55	21	9.6	41.4	4.3
11	166	141	4.9	1.4	2.7	0.56	0.56	21	7.6	24.0	3.2
12	265	158	4.7	2.0	2.7	0.79	0.56	18	18.6	52.4	2.8
13	217	118	6.0	1.3	3.2	0.37	0.41	27	7.2	28.2	3.9
14	153	195	4.9	1.1	3.4	0.45	0.45	—	15.6	24.6	1.6
15	192	125	4.9	1.3	3.3	0.47	0.26	28	5.2	12.0	2.3

CFR = coronary flow reserve; EF = ejection fraction; FV1 = mean basal coronary flow velocity; FV2 = mean hyperemic coronary flow velocity; LA = left atrial dimension; LVEDP = left ventricular end-diastolic pressure; LVIDI = indexed left ventricular internal dimension at end-diastole; LVMI = indexed left ventricular mass; MAP = mean arterial pressure; mCVR = indexed minimal coronary vascular resistance; PWT = posterior wall thickness; RWT = relative wall thickness.

diabetes mellitus, obesity and chronic renal insufficiency may affect the findings.[20-22] Our earlier work[12] pointed out that abnormalities in thallium scans and coronary vasodilator reserve are frequent findings in a hypertensive population referred for evaluation of ischemic heart disease. This larger study confirms those findings, but more specifically investigates clinical and coronary blood flow features found in those with severe LV hypertrophy.

Clinical characteristics of severe hypertensive left ventricular hypertrophy: It is interesting to note that blacks are overrepresented in the group with severe hypertrophy (67%). This is particularly striking when the presence of caucasians in the 2 control groups, represented by 83 and 53%, were compared. Increased severity of hypertension in blacks has been noted before.[23,24] Gender did not appear to play a significant role in progression to severe LV hypertrophy.

Thallium perfusion scans were positive in 73% of those with severe LV hypertrophy versus 10% in the normotensive ($p = 0.004$) and 30% in the hypertensive ($p = 0.01$) control group. These differences are highly statistically significant. The high prevalence of abnormal resting electrocardiographic and stress thallium perfusion scans in severe LV hypertrophy in the absence of significant obstructive coronary atherosclerosis is consistent with ischemia secondary to LV hypertrophy. Overall, 13 of 15 patients in the group with severe hypertrophy demonstrated clinical or laboratory evidence of major hypertensive end-organ damage resulting in depressed organ function affecting the central nervous system, the kidneys and the heart Treatment of hypertension is known to decrease mortality from stroke[25,26] but less certainly affects cardiovascular mortality.[27,28] We found that in a group believed to represent advanced hypertensive heart disease, there was a high prevalence of other associated end-organ damage, sometimes of moderate to severe degree. These other diseases may be relatively more lethal as exemplified by patient 1 from the severe hypertrophy group (Table II). This patient had severe hypertensive LV hypertrophy with a mildly depressed ejection fraction and a severely elevated LV end-diastolic pressure. Her electrocardiogram showed LV hypertrophy with strain and she had a markedly depressed coronary flow reserve but no significant coronary artery disease despite recurrent severe angina requiring multiple admissions to the hospital. She died, acutely, 2 years later of a subarachnoid hemorrhage. Other morbid outcomes in the severe hypertrophy group over the 4-year study period included progression to end-stage renal disease (patient 8), severe hypertensive episodes with recurrent mental status changes (patient 12), and development of congestive heart failure with a markedly depressed ejection fraction documented by serial echocardiographic studies (patient 15).

Morphologic, hemodynamic and coronary perfusion parameters: Almost 50% of patients with severe LV hypertrophy demonstrated moderate to severe systolic dysfunction as evidenced by depression of the ejection fraction <55%. This is probably secondary to development

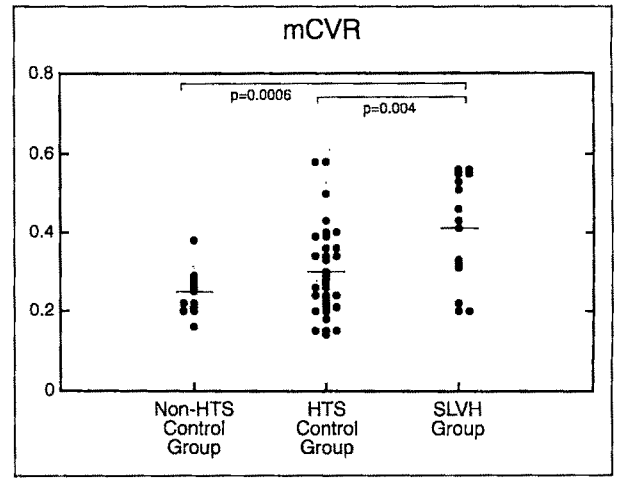


FIGURE 5. Minimal coronary vascular resistance (mCVR) indexed for basal coronary resistance in 12 nonhypertensive (HTS) control patients, 34 hypertensive control patients, and 15 hypertensive patients with severe left ventricular hypertrophy (SLVH).

of fibrosis as a result of chronic nonatherosclerotic myocardial ischemia. Typically basal coronary flow velocity is increased while peak hyperemic flow velocity is unchanged in patients with severe hypertrophy (patients 1, 6, 8 and 14). These coronary perfusion changes are believed to be caused by the increased basal flow requirements of a severely hypertrophied left ventricle in the setting of an elevated blood pressure. However, the flow reserve available for higher metabolic demand is lessened proportionately, leading to a depressed coronary flow reserve. Some patients with a depressed ejection fraction have basal flow velocities in the normal range, while peak hyperemic flow velocities may be low or normal (patients 5, 13 and 15). This pseudonormalization of basal coronary flow velocity is probably secondary to increasing amounts of fibrous tissue, which have lower metabolic requirements or alternatively secondary to myocyte hypofunctioning, hibernation or "exhaustion." [29] Increasing fibrous tissue not only stiffens the left ventricle but also alters vasoreactivity.[30] This may explain decreased peak hyperemic coronary flow velocities in some. Although LV systolic impairment is intuitively expected in severe LV hypertrophy, there is probably a transition period in which ejection fraction is low to normal. In these patients, basal flow velocities may be high (patient 12) but are often in the normal to mildly elevated range (patients 4, 10 and 11), whereas peak hyperemic flow velocities remain in the normal range. Thus, coronary flow reserve may be normal during this intermediate stage, especially when mean arterial pressure is high. Whereas most patients with severe hypertrophy have depressed or low normal ejection fractions, some may have clearly normal values (≥0.60) as did 27% in our study. This reflects the heterogeneous clinical spectrum found in hypertensive heart disease even in advanced stages of hypertrophy and may be in part related to differences in myocardial afterload.

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Impact of Left Ventricular Hypertrophy on Blood Pressure Responses to Exercise

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It is claimed that exaggerated blood pressure (BP) responses to exercise are predictive of future hypertension and may also be indicative of left ventricular (LV) hypertrophy. The relation between LV hypertrophy and maximal exercise BP was examined in 35 normal male volunteers and 65 untreated hypertensive male patients. Multiple stepwise regression analysis revealed that preexercise systolic BP was the major determinant of maximal exercise systolic BP ($r = 0.52$; $p \leq 0.0001$), indicating that higher baseline BP predicted higher exercise BP. However, hypertensive patients with LV hypertrophy had the smallest increases in systolic BP with exercise. Accordingly, there was an inverse relation between LV muscle mass and systolic BP responses to exercise in these patients ($r = -0.34$; $p = 0.005$). When compared with normotensive subjects, hypertensive patients had lower measures of maximal oxygen uptake and exercise heart rates ($p = 0.01$). This may indicate lower cardiac performance at maximal exercise and explain the reduced capacity of hypertensive patients with LV hypertrophy to increase systolic BP with exercise. Neither baseline nor exercise BPs correlated with LV mass; instead, the model of regression analysis indicated that body weight was the principal determinant of LV mass. Contrary to previous reports, exaggerated exercise BPs were not associated with LV hypertrophy in hypertensive or normotensive patients.

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Hypertension and left ventricular (LV) hypertrophy are predictors of premature cardiovascular morbidity and mortality.[1–3] Normotensive subjects who generate a maximal systolic blood pressure (BP) >200 mm Hg during exercise testing are considered at increased risk for the future development of hypertension.[4–9] It was suggested that exercise systolic BP is superior to resting systolic BP in predicting LV mass[10] and that LV hypertrophy is associated with exaggerated exercise systolic BP.[10–18]

Unfortunately, it is difficult to reach firm conclusions regarding the relations between LV mass and exercise BP. Normotensive[10,11] and hypertensive[13] patients were evaluated in separate studies, thereby making it difficult to define normal or exaggerated BP responses. It is also difficult to interpret exercise BP in hypertensive patients with coexisting diseases or who are undergoing or have recently undergone antihypertensive therapy.[13] The absence of standardized exercise protocols and the use of different protocols within the same study[10] further complicates exercise BP interpretation.

In this study we examined the influence of LV mass on BP at maximal exercise. We studied 35 normotensive volunteers and 65 hypertensive patients without known concomitant diseases and who were not receiving antihypertensive medication for ≥3 months. Unlike previous studies, we did not find an association between LV hypertrophy and increased exercise BP. Instead, preexercise systolic BP was the chief predictor of maximal systolic BP during exercise.

METHODS

One hundred male volunteers participated in the study after giving written informed consent. Subjects were free of all cardiovascular disease with the exception of uncomplicated, essential mild to moderate hypertension. Furthermore, all hypertensive patients were either newly diagnosed or not receiving antihypertensive medication for ≥3 months before enrollment in the study. Arterial BP was determined with conventional sphygmomanometry at each of 3 separate clinical visits. Subjects were allowed 3 minutes of rest in the seated position before 2 BPs (obtained a minute apart) were determined using first and fifth phase Korotkoff sounds. BPs from the 3 visits were averaged, and participants with a mean diastolic BP >90 mm Hg were considered hypertensive.

Cardiopulmonary exercise stress testing: Two cardiopulmonary exercise tests (separated by an interval of 7 to 14 days) were performed by each patient. The first test (modified Balke Ware protocol) was performed to familiarize subjects with the treadmill protocol and the

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concomitant respiratory gas analysis for the direct measurement of maximal oxygen uptake.

The second cardiopulmonary exercise stress test used a ramp treadmill protocol. This was recently described by our laboratory.[14] Briefly, after a 1-minute warm-up (2.0 mph at 0% grade), both the rate of change in treadmill speed and grade were individualized to yield a work rate over 10 minutes corresponding to the maximal oxygen uptake determined in the first test. During each test, the electrocardiogram was continually monitored and recorded at 1-minute intervals with a Marquette Electronics Inc. Case 12 electrocardiographic system. Respiratory gas exchange parameters were determined continuously using a calibrated Medical Graphics Corporation 2001 system. BPs were determined at rest (patient standing on treadmill), in the last 30 seconds of each 2-minute period, and immediately after termination of the exercise test. The same 2 auscultators (DHGS and JMN) measured exercise BP by standard sphygmomanometry throughout the study.

Patients were asked to score their perceived level of exertion by pointing to a number on the 6 to 20 Borg scale[15] at the end of each minute of exercise. All patients were encouraged to exercise to their maximal ability. Echocardiographic findings were unknown at the time of testing. Hemodynamic and gas exchange measurements obtained from the second test were analyzed in this study. Maximal exercise BP and heart rate were measured immediately after termination of the exercise test. Exercise-induced changes in BP and heart rate were determined by subtracting resting BP and heart rate values from those obtained at maximal exercise. Patients testing positive for coronary artery disease on the first treadmill were excluded from this study.

Echocardiography: M-mode and 2-dimensional echocardiograms were recorded from standard parasternal and apical windows using a commercially available phased-array echocardiograph (General Electric, Pass II or RT500 Milwaukee, Wisconsin). M-mode echocardiograms were recorded on strip chart paper at a speed of 50 mm/s, and measurements were determined according to the recommendations of the American Society of Echocardiography.[16] All measurements were obtained by 1 observer (WFG) who was unaware of the BP levels of the subject under review. M-mode tracings were only accepted for measurement after 2-dimensional analysis revealed normally functioning cardiac valves and normal LV contractile patterns. LV mass was calculated from the formula of Troy[17]: LVM (g) = $1.05 \cdot ([LVID + IVS + PWT]^3 - [LVID]^3)$, where LVID, IVS and PWT refer to the end-diastolic dimensions of the LV internal diameter, interventricular septal and posterior wall thickness, respectively. Using Framingham Heart Study normative reference data[18] and the recommendation that LV mass be indexed by height instead of body surface area, LV hypertrophy was considered present if the LV mass (g) by height (m) index exceeded 163 g/m.[19]

Duration of the study: Clinical evaluation and BP determinations, echocardiography and the 2 cardiopulmonary stress tests were completed within a 3 week period in each patient.

Statistical analysis: Statistical comparisons between normotensive and hypertensive subjects with and without LV hypertrophy were obtained by 2-way analysis of variance. Comparisons involving 2 groups of unpaired data were made with 2-tailed unpaired Student *t* tests using combined or separate variance estimates of the *t* statistic as indicated by an f test. Frequencies were analyzed by the chi-square statistic with Yates correction, as necessary. Multiple stepwise regression analysis was performed to determine the strongest correlates of exercise systolic BP and LV mass. A p value <0.05 was considered significant. Results are expressed as mean ± SEM.

RESULTS

One hundred men (mean age 45 ± 1.4 years, range 19 to 73) were studied. Anthropometric measurements and clinical BPs are listed in Table I. Patients with LV hypertrophy were heavier and had higher body mass indexes and larger body surface areas than those without hypertrophy. Hypertensive patients with LV hypertrophy had significantly higher systolic BPs ($p = 0.035$) than those without hypertrophy.

Exercise BPs, heart rates and maximal oxygen uptake (VO_2max) are listed in Table II. Higher exercise BPs and lower measurements of maximal heart rate, heart rate changes and VO_2max were found in hypertensive subjects. These differences persisted when 2-way analysis of variance was repeated with age as a covariate. Normotensive and hypertensive subjects with LV hypertrophy did not generate higher exercise BPs than their nonhypertrophic counterparts. However, all normotensive and hypertensive subjects without LV hypertrophy produced similar increments in systolic BP with exercise, despite differences in their preexercise BPs, whereas those with both hypertension and LV hypertrophy had significantly smaller increments in systolic BP with exercise.

Multiple stepwise regression analysis was used to determine the best predictors of LV mass and maximal exercise systolic BP. Variables selected to predict LV mass were: age, weight, body mass index and surface area, clinical, pre- and maximal exercise BPs and heart rates, BP and heart rate changes associated with exercise, and VO_2max. Body weight was the major correlate of LV mass for all patients ($r = 0.40$; $p < 0.001$), as well as for hypertensive ($r = 0.55$; $p = 0.0006$) and normotensive ($r = 0.37$; $p = 0.002$) subsets. Furthermore, increases in systolic BP with exercise were inverse correlates of LV mass in hypertensive patients ($r = -0.24$; $p = 0.005$).

Variables chosen to predict maximal exercise systolic BP were: age, weight, body mass index and surface area, clinical and preexercise BPs and heart rates, and LV mass. For the entire group of patients, and the normotensive and hypertensive subsets, clinical and preexercise systolic BPs and body mass index were correlates of maximal exercise systolic BP. In hypertensive patients, LV mass was an additional and inverse correlate of maximal exercise systolic BP ($r = -0.28$; $p = 0.02$).

The proportions of hypertensive patients with systolic BP levels >210 mm Hg and diastolic BP levels >90

TABLE I Anthropometric and Clinical Blood Pressure Measurements

	Normotensive		Hypertensive		
	No LVH	LVH	No LVH	LVH	ANOVA
No. of pts.	22	13	46	19	
Age (yrs)	40 ± 3	46 ± 2	45 ± 2	46 ± 3	
Weight (kg)	80 ± 2	89 ± 3*	85 ± 2	91 ± 3*	a
Body mass index ($kg \cdot m^{-2}$)	27 ± 2	32 ± 2	32 ± 1	35 ± 3	a
Body surface area (m^2)	2 ± 0.3	2 ± 0.4	2 ± 0.2	2 ± 0.4	a
Systolic BP	120 ± 3	122 ± 2	141 ± 2	151 ± 4*	a
Diastolic BP	81 ± 1	82 ± 2	97 ± 1	99 ± 1	c
Heart rate	68 ± 2	63 ± 3	72 ± 1	72 ± 2	b

*Significant differences by *t* test ($p < 0.05$) between patients with and without LVH in each normotensive and hypertensive group.
Values are mean ± SEM.
a = differences between patients with and without LVH without regard to hypertensive status ($p \leq 0.05$); ANOVA = results of 2-way analysis of variance; b = significant differences between normotensive and hypertensive patients without regard to LVH ($p \leq 0.05$); BP = blood pressure; c = significant differences by design; LVH = left ventricular hypertrophy.

TABLE II Maximal Exercise Blood Pressure and Heart Rate, and Maximal Oxygen Uptake in 100 Male Patients

	Normotensive		Hypertensive		
	No LVH	LVH	No LVH	LVH	ANOVA
Maximal systolic BP	190 ± 4	192 ± 5	203 ± 4	202 ± 4	b
Δ Systolic BP	58 ± 4	58 ± 5	56 ± 3	45 ± 4*	
Maximal diastolic BP	78 ± 2	85 ± 3	92 ± 2	94 ± 3	b
Δ Diastolic BP	−8 ± 2	−3 ± 2	−6 ± 2	−9 ± 2	
Maximal heart rate	176 ± 3	170 ± 5	166 ± 2	161 ± 4	b
Δ Heart rate	98 ± 4	96 ± 4	84 ± 3	84 ± 4	b
VO_2 max	40 ± 2	39 ± 3	32 ± 1	32 ± 2	b
Test duration (s)	636 ± 23	632 ± 19	593 ± 17	602 ± 26	
Perceived effort (Borg scale)	19 ± 0.2	19 ± 0.4	19 ± 0.2	19 ± 0.3	

VO_2 max = maximal oxygen uptake; Δ = change with exercise; other abbreviations and symbols as in Table I.

mm Hg at maximal exercise were 46 and 66%, respectively. This was significantly larger ($p = 0.01$) than the 14 and 26% of normotensive patients who exceeded these BP criteria, respectively. Thus, higher baseline BP was associated with higher exercise BP. In contrast, the presence of LV hypertrophy was not associated with a larger proportion of patients exceeding these BP levels at maximal exercise.

DISCUSSION

We found that high baseline BP is the chief predictor of high exercise BP. Contrary to previous reports,[10,11,13] this study did not find an association between LV hypertrophy and exaggerated exercise BP. Indeed, hypertensive patients exhibited inverse relations between LV mass and the increase in systolic BP with exercise. Hypertensive patients with LV hypertrophy had smaller increases in systolic BP with exercise than did those without hypertrophy. Moreover, compared with normal volunteers, hypertensive patients had lower measures of maximal oxygen uptake and heart rate at maximal exercise. Because VO_2max is an indirect estimate of cardiac output at maximal exercise, this raises the possibility that hypertensive patients may have a limited ability to exhibit a full, hemodynamic response to maximal treadmill exercise. This appears most marked when hypertension and LV hypertrophy coexist.

The results of the present study were clearly different from those reported previously.[10,11,13] Unfortunately, the earlier attempts to determine whether exercise BP responses were predictive of future hypertension used differing exercise protocols.[9] Moreover, exercise BP end points chosen to identify patients with LV hypertrophy or an increased risk of future hypertension were inconsistent. For example, maximal exercise systolic BP end points ranged from 200 to 230 mm Hg.[4–13]

The effects of coexisting diseases and concurrent antihypertensive medications on exercise BP and LV mass may further explain the differing results between a previous report and the present study.[13] Because treatment may influence LV mass[20] and the response of BP to exercise,[21] the inclusion of patients receiving antihypertensive medication may have reflected differing treatment effects rather than the influence of LV mass on exercise BP. Another potential cause of inconsistency is the difficulty of obtaining accurate measurements of exercise BP. This is particularly true in patients who require high work loads to achieve maximal exercise levels. Performance during exercise testing may also be affected by the degree of familiarity with the exercise test procedure. Unfamiliarity with the exercise protocol may induce anxiety and affect BP changes; it can also result in submaximal exercise performances. Previous reports[10,11,13] describing an association between exaggerated exercise BP and LV hypertrophy did not include a learning exercise test.

In the present study we attempted to minimize these confounding factors. All patients underwent a preliminary test to gain familiarity with exercise testing procedures; for the definitive second test, all patients were exercised to maximal effort at individualized work rates during a 10-minute period; each of the patient groups

recorded the same level of perceived exertion at maximal exercise; the same observers measured exercise BP throughout the study; and hypertensive patients were either newly diagnosed or not receiving antihypertensive medication for ≥3 months.

This carefully performed study did not confirm previous claims relating the presence of LV hypertrophy to exaggerated exercise BP in normotensive or hypertensive patients. Rather, we showed that the principal determinant of systolic BP response to exercise is preexercise systolic BP.

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Hemodynamic and Metabolic Effects of Intravenous Clentiazem in Hypertensive Patients

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To determine the hemodynamic and certain metabolic effects of clentiazem, a diltiazem congener, 10 untreated essential hypertensive patients were given the calcium antagonist in 3 successive doses totaling 1.0 mg/kg intravenously. Mean arterial pressure and total peripheral resistance progressively declined from 121 ± 3 mm Hg and 47 ± 2 U (mean) to 110 ± 3 mm Hg and 33 ± 1 U, respectively ($p < 0.05$); heart rate remained unchanged. Cardiac output increased as a result of augmented cardiopulmonary volume ($p < 0.05$) produced by peripheral venoconstriction and norepinephrine release (from 258 ± 41 to 319 ± 42 pg/ml; $p < 0.01$). Surprisingly, there was an immediate reduction in plasma aldosterone (10.4 ± 1.2 to 6.5 ± 1.0 ng/dl; $p < 0.01$), serum potassium (4.3 ± 0.1 to 3.6 ± 0.1 mEq/dl; $p < 0.001$) and calcium (9.5 ± 0.1 to 8.8 ± 0.1 mg/dl; $p < 0.001$) concentrations, whereas epinephrine increased (21.2 ± 3.3 to 45.8 ± 5.9 pg/ml; $p < 0.002$). Previous studies with diltiazem, conducted similarly, did not show these changes. Therefore, clentiazem reduced mean arterial pressure through a decrease in total peripheral resistance, and released epinephrine was associated with intracellular potassium influx (urinary potassium did not change). The inhibited aldosterone release was not compensated by altered renal blood flow, glomerular filtration or increased plasma renin activity. These findings underscore the concept that calcium antagonists are a remarkably heterogeneous antihypertensive group.

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The hemodynamic hallmark of essential hypertension is an elevated arterial pressure that is associated with an increased total peripheral resistance that is more or less uniformly distributed throughout most organ circulations.[1–4] The calcium antagonists reverse these hemodynamic alterations.[5–8] A new compound, clentiazem, is an 8-chloro analog of diltiazem, which has only been evaluated in the hypertensive rat[9,10] but not in hypertensive patients.

METHODS

Patients: Ten patients (6 men, 6 white) with mild to moderately severe essential hypertension, whose ages ranged from 48 to 69 years (average 58 ± 2), were the subjects of this study. The mean (±1 SEM) age was 58 ± 2 years, average body weight 85 ± 6 kg, and body surface area was 2.0 ± 0.09 m^2. Detailed clinical evaluation failed to reveal a secondary cause for their hypertension. Patients were enrolled if their supine diastolic pressure was 90 to 115 mm Hg after discontinuation of all medication for ≥2 weeks. Informed consent of the protocol, previously approved by our institutional clinical investigation committee, was obtained from all patients before entrance into the study.

Hemodynamic assessment: The study was performed in 2 days. On the first day, when the subjects had been without drugs for ≥2 weeks, blood pressure and heart rate were measured indirectly, 12-lead electrocardiographic, M-mode and 2-dimensional echocardiographic examinations were performed at rest, and splanchnic and renal blood flows and plasma volume were determined.[5] Blood was also obtained to measure plasma renin activity and plasma aldosterone, and serum epinephrine and norepinephrine concentrations. The patients were then instructed to begin a 24-hour urine collection and to return on the following day. On the second day, after an overnight fast, the patient was studied in the hemodynamic laboratory. With use of a modified Seldinger technique, catheters were inserted into a brachial artery and an antecubital vein and advanced to the shoulder level to permit continuous recording of arterial and venous pressures simultaneously with the electrocardiogram (lead II).[11] Cardiac output was obtained at least in triplicate, using indocyanine green dye (5 mg each injection); central blood (i.e., cardiopulmonary) volume was calculated as the blood flow per second times mean transit time.[12]

Thus, resting, supine hemodynamic measurements were obtained after intravenous administration of placebo and after sequential intravenous bolus administration of clentiazem (0.025, 0.025, and 0.05 mg/kg). Five minutes after each dose was administered, arterial and venous pressures with electrocardiogram were recorded,

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TABLE I Immediate Hemodynamic and Humoral Effects of Clentiazem

Systemic Hemodynamics	Control	Dose of Intravenous Drug (mg/kg)		
		0.025	0.025	0.05
Arterial pressure (mm Hg)				
Systolic	176 (5)	171 (5)	168 (4)*	163 (4)*
Diastolic	94 (3)	87 (3)*	88 (3)*	84 (3)*
Mean	121 (3)	115 (3)*	114 (3)*	110 (3)*
Heart rate (beats/min)	65 (3)	67 (3)	67 (2)	69 (2)
Cardiopulmonary volume (liters)	2.4 (0.3)	2.4 (0.2)	2.5 (0.2)	2.6 (0.2)*
Cardiac index (liters/min/m^2)	2.6 (0.1)	2.9 (0.1)	3.0 (0.1)*	3.4 (0.1)*
Stroke index (ml/m^2)	41 (2)	44 (2)	46 (2)*	49 (2)*
Total peripheral resistance index (U/m^2)	47 (2)	40 (2)	38 (2)*	33 (1)*
Ejection time (ms)	304 (11)	299 (9)	294 (9)	300 (9)
Total blood volume (ml)	4,994 (352)	—	—	4,574 (397)
Plasma volume (ml)	3,230 (256)	—	—	2,857 (251)
Renal				
Renal blood flow (ml/min)	761 (92)	—	—	919 (87)*
Renal vascular resistance (U)	18.4 (2.4)	—	—	13.5 (1.8)*
Glomerular filtration rate (ml/min)	87.4 (13)	—	—	86.8 (13)
Filtration fraction (%)	18.2 (2.0)	—	—	15.8 (2.5)
Splanchnic (9 patients)				
Splanchnic blood flow (ml/min)	679 (64)	—	—	590 (50)
Splanchnic vascular resistance (U)	19.8 (2.2)	—	—	20.1 (1.9)
Humoral effects				
Norepinephrine (pg/ml)	258 (41)	—	—	319 (42)‡
Epinephrine (pg/ml)	21.2 (3.3)	—	—	45.8 (5.9)§
Aldosterone (ng/dl) (5 patients)	10.4 (1.2)	—	—	6.5 (1)†
Plasma renin activity (ng/ml/hour)	0.87 (0.11)	—	—	1.08 (0.24)

*$p < 0.05$; †$p < 0.02$; ‡$p < 0.01$; §$p < 0.002$ compared with control.
Results are expressed as mean ± SEM.

and cardiac output was obtained. Then the next dose was administered and the same hemodynamics were obtained. After the last dose, all measurements including systemic, renal and splanchnic hemodynamics with plasma volume determination and blood sampling for chemistries and humoral agents were repeated including initiation of a second 24-hour urine collection. Hemodynamic responses to 5 minutes of upright tilt (50°), isometric exercise (handgrip, 30% of maximum) and Valsalva maneuver were measured before and after intravenous administration of clentiazem.

Echocardiography: Two-dimensionally guided M-mode echocardiograms (Toshiba, SSH 60-A, 2.5 and 3.75 MHz) were obtained before and after administration of each dose of clentiazem in order to determine resting cardiac anatomic and functional indexes. These echocardiograms were interpreted by 2 independent observers unaware of the phase of study. Patients were studied in the recumbent half-left lateral position. Left ventricular wall thickness and dimensions were measured according to standard criteria.[13] Left ventricular volumes were calculated according to the Teichholz formula,[14] and left ventricular mass (American Society of Echocardiography corrected cube formula) was calculated.[15] Left ventricular function was assessed by calculating ejection fraction, fractional fiber shortening, velocity of circumferential fiber shortening, and the contractility index (end-systolic wall stress/end-systolic volume index).[16]

Regional hemodynamics: Renal plasma flow and plasma volume were determined by the single injection clearance of ^{131}I-paramino hippurate and radioiodinated serum albumin-^{125}I, respectively.[11] Splanchnic blood flow was obtained by plasma clearance of injected indocyanine green dye (50 mg).[11] Renal and splanchnic vascular resistances were calculated by dividing mean arterial pressure by the respective blood flows. Glomerular filtration rate was determined from 24-hour creatinine clearance and renal filtration fraction by dividing glomerular filtration rate by renal blood flow.

Total blood volume and red cell mass were estimated from plasma volume.[17] Plasma renin activity and catecholamine levels were determined by the methods of Sealey et al[18] and Peuler and Johnson,[19] respectively. Aldosterone was determined by the radioimmunoassay technique.[20]

Statistical analysis: One-way analysis of variance with repeated measures was used to compare baseline with hemodynamic effects of sequential doses of clentiazem. Subsequent to significance tests, Bonferroni's test was used to make pairwise comparisons between baseline and treatment values. Where appropriate, paired Student's *t* test was used to make comparisons.[21]

RESULTS

Hemodynamics: After administration of clentiazem, total peripheral resistance was reduced, thereby significantly decreasing systolic, diastolic and mean arterial pressures. The cardiac index remained stable after the first dose, but increased with the second and third doses in proportion to the increase in venous return, and cardiopulmonary and stroke volumes; heart rate remained unchanged (Table I). These changes no doubt reflect the increase in circulating catecholamine levels in re-

sponse to the decrease in arterial pressure (Table I). There were no changes in cardiac function or in structure (Table II).

Intravenous clentiazem also significantly decreased renal vascular resistance and increased renal blood flow; glomerular filtration rate and filtration fraction and splanchnic hemodynamics remained unchanged (Table I). Moreover, the responses to physiologic maneuvers remained unaltered (Table III).

Metabolic changes: Serum sodium, creatinine, uric acid concentrations, and 24-hour urinary volume and sodium and potassium excretion remained unchanged. In contrast, serum potassium and calcium concentrations significantly decreased while chloride concentration increased (Table IV). Plasma aldosterone concentration also decreased significantly, although there were no changes in plasma renin activity or intravascular volume (Table IV).

TABLE II Cardiac Structure and Function Before and After Clentiazem

	Control	Intravenous Drug
Posterior wall thickness (cm)	1.2 (0.1)	1.2 (0.1)
Septal thickness (cm)	1.3 (0.1)	1.2 (0.1)
Left ventricular mass (g)	254 (29)	263 (27)
Left ventricular internal diastolic diameter (cm)	5.0 (0.3)	5.2 (0.3)
Left ventricular internal systolic diameter (cm)	3.3 (0.2)	3.5 (0.3)
Ejection fraction (%)	64 (3)	61 (4)
Fractional fiber shortening of the left ventricle	35 (2)	34 (3)

DISCUSSION

Clentiazem is a derivative of diltiazem, having a longer half-life and is approximately 3 times as potent as its congener on a weight basis.[9,10] Our earlier studies in both normotensive and hypertensive rats demonstrated that the decrease in arterial pressure resulted from arteriolar dilatation which produced a decrease in total peripheral resistance and dilatation of target organ circulations.[9,10] Furthermore, this compound demonstrated a profound intrarenal circulatory effect that decreased efferent as well as afferent glomerular arteriolar resistance and glomerular hydrostatic pressure.[9,10] The present data confirm those previous hemodynamic findings, extending these observations to patients with mild to moderate essential hypertension. Thus, with sequentially increasing doses, clentiazem reduced arterial pressure by reducing total peripheral resistance. However, as was found with other calcium antagonists after their intravenous administration, cardiac output tended to increase, most likely based on reflex cardiac stimulation in response to the pressure reduction associated with a norepinephrine release.[5-7] However, clentiazem increased stroke volume, while diltiazem increased heart rate; the augmented stroke volume no doubt reflects an increased venous return and cardiopulmonary volume associated with norepinephrine-induced peripheral venoconstriction that shifted circulating volume to the central circulation.

Associated with the elevated cardiac output was an increased renal blood flow and a decreased renal vascular resistance without changes in glomerular filtration rate or renal filtration fraction. These renal hemodynamic changes were similar to those produced by diltiazem in a similarly designed study.[5] Since both agents increase renal blood flow without changing the glomerular filtration rate, efferent glomerular arteriolar dilatation was likely to have occurred. This was confirmed by renal micropuncture studies from our laboratory[9,10,22] and others.[23]

Clentiazem produced a highly significant decrease in serum potassium concentration ($p < 0.001$), which was not observed with its chemical analog (diltiazem).[5] This hypokalemia was observed in every patient; it was associated with other important effects including a marked increase in plasma epinephrine (21.2 ± 3.3 to 45.8 ± 59 pg/ml; $p < 0.002$) that most likely produced a rapid influx of potassium ions intracellularly, previously suggested to be associated with β_2-adrenergic receptor stimulation.[24,25]

Clentiazem also produced a profound reduction in circulating aldosterone levels; this effect also was different from those produced by diltiazem.[5] Studies in animals and in adrenal cellular suspensions have shown that calcium entry into adrenal glomerulosa cells is necessary for aldosterone synthesis.[26,27] Thus, this reduction in aldosterone may reflect a direct action of clentiazem on adrenal cells, an action not observed with its chemical congener diltiazem.[5] The reduction in potassium did not stimulate renin release, increase aldosterone secretion, and was not associated with an increased urinary potassium excretion. The reduced serum calcium concentration has been reported in another clentiazem study.[28]

Thus, despite its chemical similarity with diltiazem, clentiazem displayed several major hemodynamic and metabolic differences: (1) peripheral venoconstriction

TABLE III Responses to Hemodynamic Maneuvers Before and After Intravenous (IV) Clentiazem

Change in Hemodynamic Function (%)	Isometric Exercise		Upright Tilt (9 patients)		Valsalva	
	Placebo	IV	Placebo	IV	Placebo	IV
Mean arterial pressure (mm Hg)	18 (3)	20 (4)	0.3 (3.5)	−4 (6)	16 (3)	17 (4)
Cardiac index (ml/min/m^2)	5 (3)	6 (5)	−19 (3)	−18 (3)	—	—
Heart rate (beats/min)	13 (3)	16 (3)	11 (4)	18 (5)	9 (4)	2 (5)
Total peripheral resistance index (U/m^2)	13 (3)	15 (8)	23.8 (3.8)	17.7 (7.4)	—	—

Results are expressed as mean ± SEM of percent change in the supine resting responses as compared with pre-maneuver levels.

TABLE IV Acute Effects of Intravenous Clentiazem on Blood Chemistries

Laboratory Measurements	Control	Treatment
Plasma sodium (mEq/liter)	141 (0.4)	141 (0.6)
Plasma potassium (mEq/liter)	4.3 (0.1)	3.6 (0.1)*
Plasma chloride (mEq/liter)	101.5 (0.5)	107 (1)†
Plasma calcium (mEq/liter)	9.48 (0.1)	8.79 (0.1)*
Phosphorus, inorganic (mg/dl)	3.40 (0.2)	3.0 (0.2)
Plasma glucose (mg/dl)	98.2 (3)	93.6 (3)
Plasma uric acid (mg/dl)	4.4 (0.3)	4.4 (0.3)
Plasma creatinine (mg/dl)	1.11 (0.1)	1.13 (0.2)
Urine volume (ml)	1360 (165)	1297 (116)
Urine potassium (mEq/liter)	47.1 (6)	43.6 (8)
Urine sodium (mEq/liter)	122 (18)	110 (15)
Urine creatinine (mg/24 hour)	1377 (205)	1303 (193)

*p <0.05; †p <0.001.
Results are expressed as mean ± 1 SEM.

shifting circulating blood centrally to increase cardiac output; (2) adrenal release of epinephrine in addition to neural release of norepinephrine in response to (or in association with) arterial hypotension; (3) hypokalemia most likely produced by the twofold increase in epinephrine; (4) reduced aldosterone levels unassociated with diminished levels plasma renin activity, intrarenal hemodynamics or hyperkalemia; and (5) hypocalcemia. These findings underscore the concept that calcium antagonists form a remarkably heterogeneous class of pharmacologic compounds.

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Left Ventricular Ejection Performance in Mitral Stenosis, and Effects of Successful Percutaneous Transvenous Mitral Commissurotomy

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Impaired left ventricular ejection performance was reported in pure mitral stenosis. The speculative mechanisms included insufficient preload, increased wall stress, high right ventricular pressure and unknown myocardial factors, but no definitive mechanism has been established.

Fifteen patients with tight mitral stenosis who underwent successful percutaneous transvenous mitral commissurotomy were studied to ascertain whether ejection performance would improve with sufficient blood filling. The indexes of preload (end-diastolic volume) and ejection performance (stroke volume, ejection fraction, and mean systolic and mean normalized ejection rates) were calculated angiographically before and immediately after mitral commissurotomy. Improved blood filling (the result of successful mitral commissurotomy) produced an increase in end-diastolic volume (mean ± SD 99.0 ± 30.2 to 112.1 ± 30.1 ml/m^2; $p < 0.05$). All 4 indexes of ejection performance also improved. There was good correlation between end-diastolic and stroke volumes before intervention (stroke volume = 0.476 × end-diastolic volume + 16.77; r = 0.76), and the relation between them showed no change even after mitral commissurotomy.

It is concluded that both left ventricular preload and ejection performance improved after successful percutaneous transvenous mitral commissurotomy. Insufficient preload could affect ejection performance in patients with tight mitral stenosis.

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Left ventricular ejection performance is often reduced in mitral stenosis.[1–4] Suspected causes include insufficient preload, afterload mismatch,[5,6] the effects of high right ventricular pressure,[7] and unknown myocardial factors.[8,9] However, the precise mechanism has not been established. The pure effects of mitral obstruction on ejection performance could not be assessed by standard means after open chest surgery[8–10] or in comparison with normal subjects,[3,4] because other factors such as contractility and loading conditions could not be kept constant. Recently, percutaneous transvenous mitral commissurotomy permitted relief of mitral obstruction[11–13] with only modest changes in other factors.

In the present study, we evaluated left ventricular preload and ejection performance before and after percutaneous transvenous mitral commissurotomy. Unlike other studies, percutaneous technique allowed us to recognize the direct effect of mitral obstruction. The purpose of this study was to clarify whether ejection performance would improve after sufficient preload produced by mitral commissurotomy.

METHODS

Patient selection: Fifteen patients (11 women, 4 men, mean age 48 ± 10 years) with tight mitral stenosis (mitral valve area <1.5 cm^2) who underwent successful percutaneous transvenous mitral commissurotomy (1.5-fold increase in mitral valve area) using the method of Inoue et al[11] with adequate condition of the left ventriculogram were selected. Three patients had normal sinus rhythm, and the remaining 12 were in atrial fibrillation. Patients with ischemic heart disease, pericardial disease, or moderate or severe aortic valve disease were excluded from the study. Patients with moderate or severe mitral regurgitation,[14] and those who had a significant increase in mitral regurgitation[14] after mitral commissurotomy, were also excluded. All patients underwent color Doppler imaging soon after catheterization to exclude intracardiac shunting.

General methods: Each patient underwent right and left heart catheterization. The mitral valve orifice area was calculated by the Gorlin formula.[15] Biplane (30° right and 60° left anterior oblique projections) left ventriculography was performed in all patients both before and immediately after mitral commissurotomy. Left ventriculograms were recorded on 35 mm film at 50 frames/s.

TABLE I Hemodynamic Parameters Before and After Percutaneous Transverous Mitral Commissurotomy

	Before	After
Mitral valve area (cm^2)	1.1 ± 0.3	1.9 ± 0.6*
Mean diastolic pressure gradient (mm Hg)	13.1 ± 4.6	5.9 ± 2.6*
Cardiac index (liters/min/m^2)	3.2 ± 0.8	3.6 ± 1.1*
Aortic mean pressure (mm Hg)	89.4 ± 8.4	91.5 ± 11.5
Pulmonic mean pressure (mm Hg)	27 ± 8.8	17.3 ± 3*
Heart rate (beats/min)	69.8 ± 13	70.8 ± 13.2

*p < 0.05 vs before mitral commissurotomy.

Data analysis: A right oblique projection sequence in the left ventriculogram in which the RR interval was within 900 ± 200 ms and with a preceding RR interval within its 10% variance was selected. The sequences were stored in an image processing computer system (Mipron, Kontron Co. Ltd.). From end-systole to the next end-systole, left ventricular outlines were traced frame-by-frame by blinded tracer. Left ventricular volumes were calculated by the single plane Simpson's method. Each calculated volume was standardized by body surface area.

Using the left ventricular volume curve, the parameters of blood filling and ejection were calculated (Figure 1). The diastolic filling period was divided in 3 equal parts (early, mid- and late diastole). The blood volume entering the left ventricle during each period was calculated. Four indexes of ejection performance, stroke volume, ejection fraction, and mean systolic and mean normalized systolic ejection rates were calculated (Figure 1).

Statistics: All data were expressed as mean ± SD. Statistical significance was assessed by Student's paired *t* test. A p value <0.05 was considered to be statistically significant.

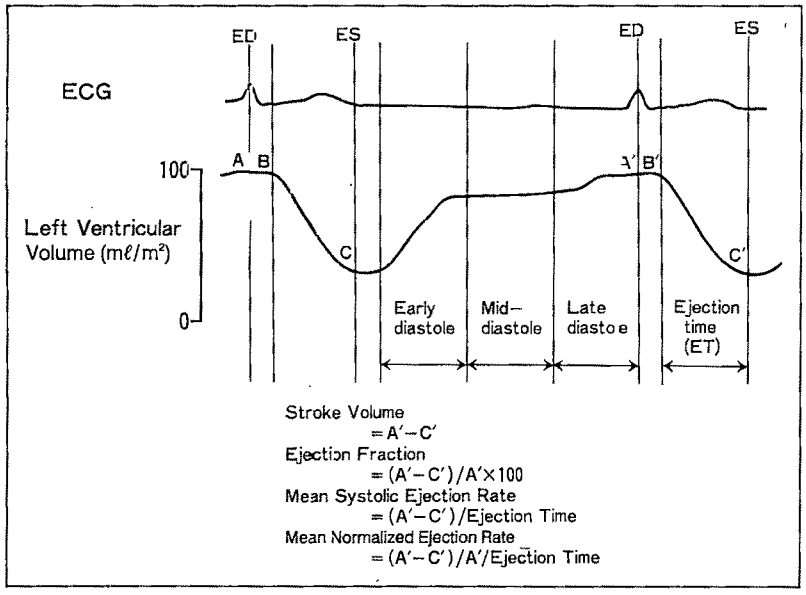


FIGURE 1. Diastolic filling and systolic ejection indexes were calculated as shown. Diastolic filling interval was divided in 3 equal parts. Blood volumes entering left ventricle during each period (early, mid- and late filling volumes) were calculated. Stroke volume and ejection fraction of next cardiac cycle were calculated. Slope of left ventricular volume curve during left ventricular ejection phase, and its normalized value by end-diastolic (ED) volume were determined as mean systolic and mean normalized ejection rates, respectively. ECG = electrocardiogram; ES = end-systole.

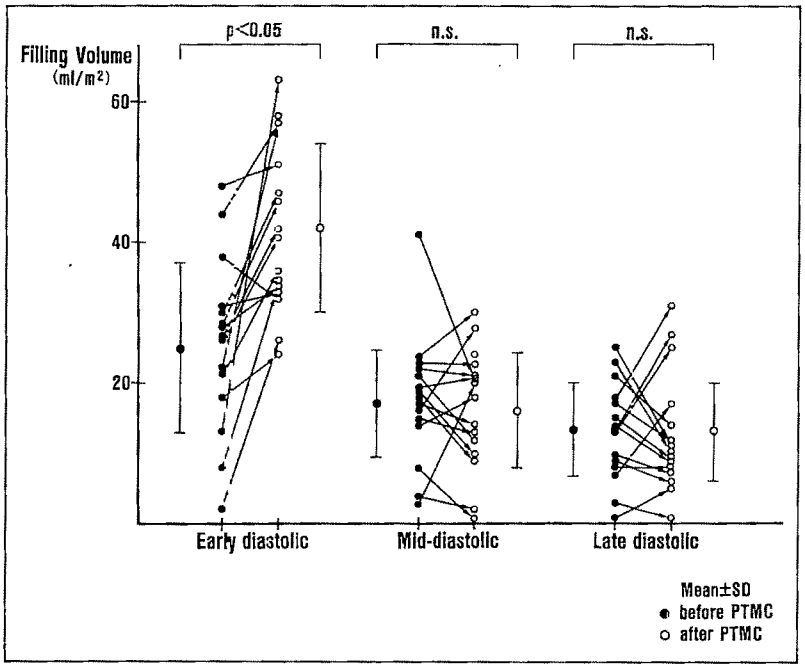


FIGURE 2. Blood volumes entering left ventricle during early, mid- and late thirds of diastolic filling period both before and after percutaneous transvenous mitral commissurotomy (PTMC). Early diastolic filling volume increased soon after PTMC. n.s. = not significant.

RESULTS

Change in hemodynamics (Table I): Successful mitral commissurotomy caused significant increases in mitral valve area and cardiac index. The pulmonary arterial mean pressure and the mean diastolic pressure gradient between the left atrium and the left ventricle decreased. The aortic mean pressure and heart rate did not change.

Change in diastolic blood filling: Figure 2 shows the changes in early, mid- and late diastolic filling volume. Although mid- and late diastolic filling volumes did not change, early diastolic filling volume increased after mitral commissurotomy. The amount of blood entering the left ventricle in 1 cardiac cycle also increased, which caused the increase in end-diastolic volume.

Change in systolic ejection performance: All the derived indexes indicated improved ejection performance after mitral commissurotomy. Ejection fraction increased from 61.2 ± 13.1 to 67.1 ± 11.4% (Figure 3). Mean systolic ejection rate increased from 305.0 ± 91.5 to 387.0 ± 29.2 ml/m^2/s (Figure 4), and mean normalized ejection rate increased from 2.1 ± 0.5 to 2.5 ± 0.6/s (Figure 5). Figure 6 shows the relation between end-diastolic and stroke volume. Both of them increased after mitral commissurotomy, and there was a linear correlation between them. The regression equations were stroke volume = 0.476 × end-diastolic volume + 16.77 (r = 0.76) before, and stroke volume = 0.477 × end-diastolic volume + 20.74 (r = 0.81) after mitral commissurotomy. There was no significant change in the relations after mitral commissurotomy.

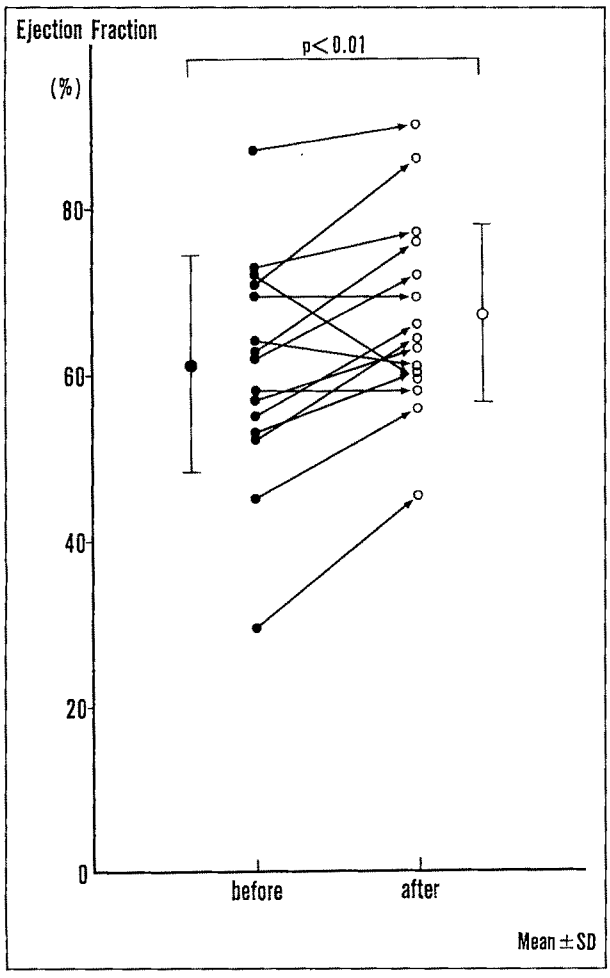


FIGURE 3. Ejection fractions both before and after percutaneous transvenous mitral commissurotomy. Ejection fraction increased significantly soon after mitral commissurotomy.

DISCUSSION

The present study demonstrated improved diastolic filling and systolic ejection after successful percutaneous transvenous mitral commissurotomy. The amount of blood entering the left ventricle during early diastole increased significantly, resulting in increases in blood filling in 1 cardiac cycle and in end-diastolic volume. Systolic ejection performance also improved soon after, suggesting an effect of insufficient preload on ejection performance in mitral stenosis.

Although many investigators reported reduced ejection performance in mitral stenosis,[3,4,10] the cause is still unknown. Many investigators assumed that insufficient preload was the cause of this systolic dysfunction. However, no studies provided clear evidence of improved ejection performance after operative procedures for mitral obstruction designed to increase preload.[8-10] In the present study, we demonstrated increased preload and ejection performance after successful mitral commissurotomy. Two explanations for the difference are possible. First, myocardial contractility and loading conditions may have changed owing to general anesthesia, chest opening or cardioplegia after the operative procedure.

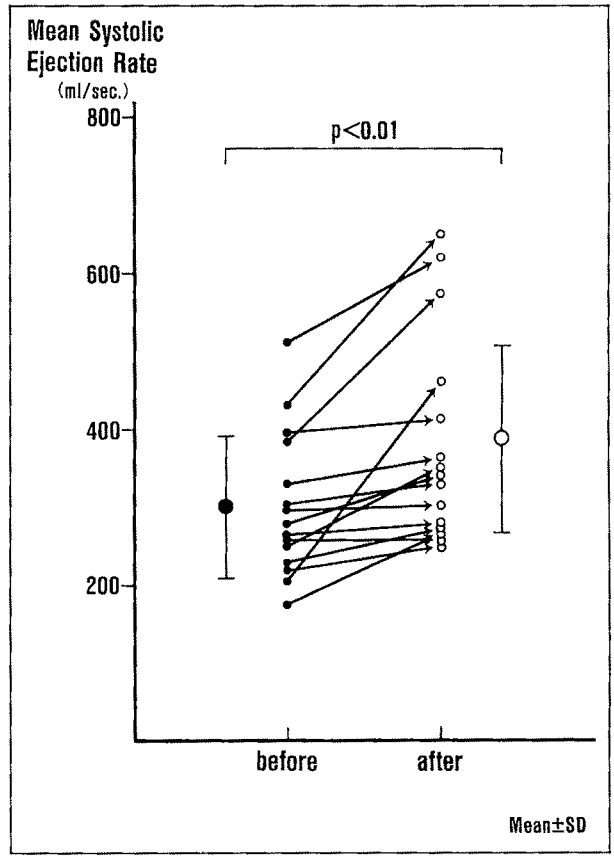


FIGURE 4. Mean systolic ejection rates both before and after percutaneous transvenous mitral commissurotomy. Mean systolic ejection rate increased significantly soon after mitral commissurotomy.

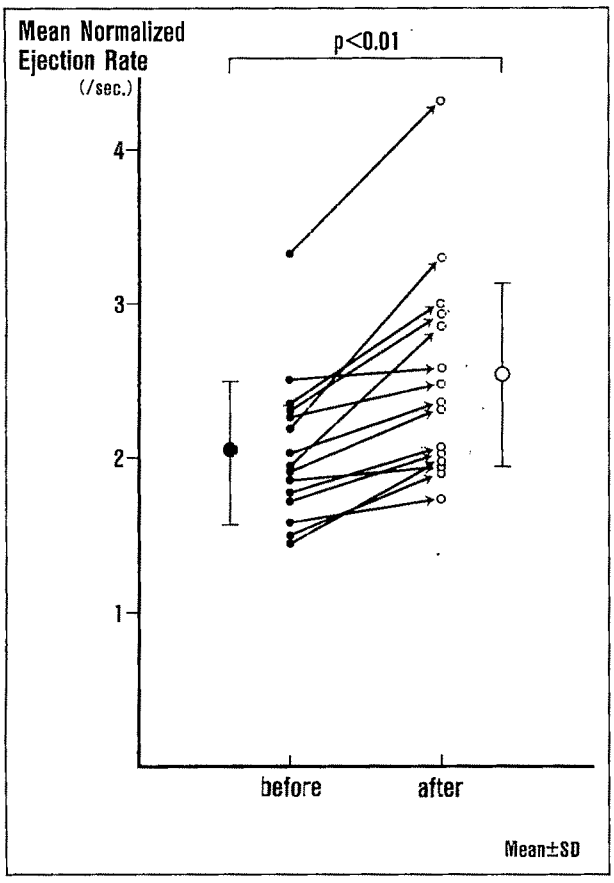


FIGURE 5. Mean normalized ejection rates both before and after percutaneous transvenous mitral commissurotomy. Mean normalized systolic ejection rate increased significantly soon after mitral commissurotomy.

However, in our study, the area of the mitral orifice increased without these changes. Second, the effect of heart rate should be considered. In previous studies, there was no strict consideration of heart rate.[8-10] In this study we analyzed cases in which the RR interval and its preceding RR interval were relatively constant in order to avoid the effects of heart rate on blood filling and ejection performance.[16]

Some investigators reported a fibrosed and shortened posterior wall in mitral stenosis,[3,17,18] and suggested that this "myocardial factor" may be the cause of systolic dysfunction. Others assumed increased systolic wall stress[5,6] or right ventricular systolic pressure[19-21] to be the cause. These previous studies are not incompatible with our findings. We have only suggested that increased preload could improve ejection performance. Some patients showed sustained ejection disturbance even after mitral commissurotomy, which suggests the involvement of other factors. Although the patient's age, initial mitral valve area, end-diastolic volume and ejection fraction, presence or absence of atrial fibrillation, and changes in right ventricular pressure may affect the results, obvious effects could not be demonstrated in this study. Furthermore, we were not able to demonstrate precisely whether myocardial contractility may change. Our data shows that the relation between stroke and end-diastolic volumes did not change after mitral commissurotomy, suggesting that ejection performance improved without a change in contractility. Further evaluation of myocardial contractility in mitral stenosis is needed.

We conclude that both left ventricular preload and ejection performance improved after successful mitral

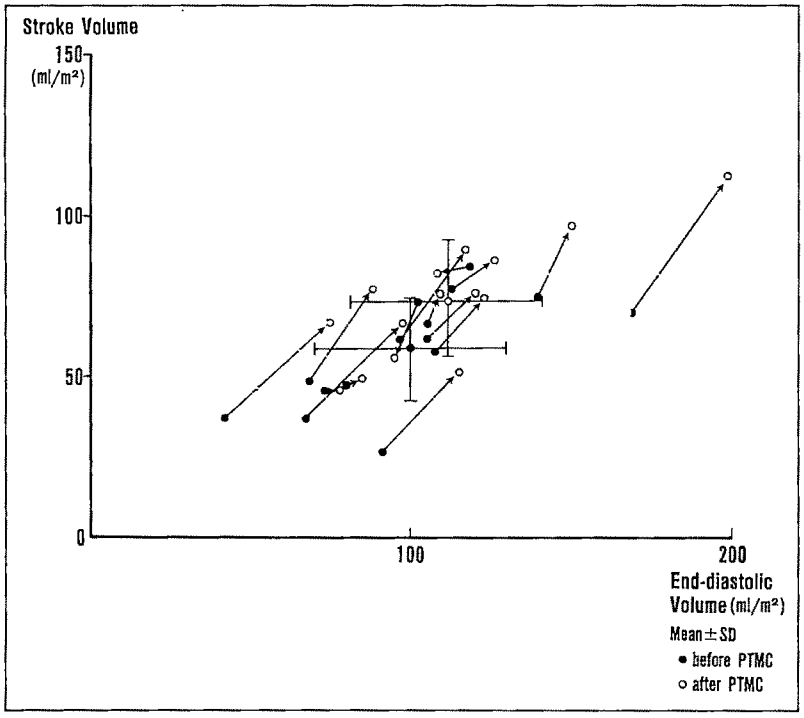


FIGURE 6. Relations between end-diastolic and stroke volumes both before and after percutaneous transvenous mitral commissurotomy (PTMC). Correlation coefficients are 0.76 before and 0.81 after PTMC. Regression equations are Y = 0.476 X + 16.77 before, and Y = 0.477 X + 20.74 after PTMC.

commissurotomy. Insufficient preload could affect ejection performance in patients with tight mitral stenosis.

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Findings on Doppler Echocardiography in Asymptomatic Intravenous Heroin Users

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To detect potential cardiac abnormalities induced by intravenous heroin use, 68 persons without a previous episode of infective endocarditis were studied by Doppler echocardiography. A control group of 41 normal subjects was studied for comparison. The following measurements were considered: (1) diameter of heart chambers, (2) systolic left ventricular function, (3) morphologic valvular abnormalities, (4) presence of valve regurgitations, (5) Doppler indexes of diastolic function, and (6) estimation of pulmonary arterial resistances. Results showed no significant differences regarding the size of the heart chambers or systolic left ventricular function. A significantly higher incidence of valvular abnormalities (focal thickening or valve prolapse) was found in drug addicts ($p = 0.0009$) at the mitral and tricuspid valves, as was valvular regurgitation detected by Doppler ($p = 0.04$). Also, a significantly prolonged deceleration time of mitral and tricuspid early diastolic Doppler flow was found in the study group ($p = 0.0001$ and 0.027, respectively) although a different hemodynamic condition in the study group (pharmacologically reduced preload) precluded these findings to be attributable to an actual diastolic dysfunction. No differences were observed in pulmonary arterial resistances. It is concluded that mitral and tricuspid valve abnormalities can be detected by echocardiography in asymptomatic intravenous heroin users, whereas no apparent effects are observed in morphologic or functional parameters of cardiac structures other than the valves.

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Infectious complications are the most frequent cause of medical attention in intravenous drug addicts[1]; one of the most fearful is infective endocarditis, typically involving the tricuspid valve.[2,3] Although most of the nonaddicted patients with endocarditis have a previous congenital or acquired valvular heart disease,[4] this is apparently not the case in drug abusers.[5] This fact has led to the opinion that in this latter group the infection of the valve takes place on an otherwise normal endocardium. The hypothesis of an abnormality of the valve induced by the drug or other accompanying insoluble substances[6] has been scarcely investigated: 1 echocardiographic study on addict patients without a history of endocarditis reported no apparent abnormalities.[7] Moreover, there is even less information on potential adverse effects of drug addiction on cardiac structures other than the valves.

In the present study, the effects on the heart of a long-standing habit of intravenous drug addiction were prospectively investigated by means of echocardiography and Doppler examination on a series of subjects without previous endocarditis.

METHODS

Patient group: A consecutive series of 71 subjects with a history of long-term addiction to intravenous heroin were studied. All subjects were following a detoxication program in a dedicated hospital-based unit. Because of the suspicion of a previous episode of infective endocarditis, 3 persons were excluded. The final study group comprised 68 patients (55 men and 13 women, age range 18 to 41 years [mean 26 ± 7]). All 71 subjects had been active consumers until their enrollment in the detoxication program; the history of addiction dated from 1 to 15 years (mean 5 ± 3.5) in doses ranging from 0.125 to 1 g, either daily or every other day. Most of the subjects admitted an occasional use of other illegal substances in the past, particularly cocaine. Repeat unsuccessful attempts at drug abstinence were frequently reported by most of the patients. At the time of the study, patients were receiving propoxyphene and triazolam, or alprazolam, in different doses, as part of the detoxication protocol. Human immunodeficiency virus antibodies were present in 29 patients (43%), although an overt clinical episode of acquired immunodeficiency syndrome had not been recorded for any patient. In all of the subjects, a complete physical examination, electrocardiogram and chest x-ray film ruled out a clinically detectable cardiac abnormality.

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Control group: A series of 41 normal persons were also studied. This control group comprised 29 men and 12 women of sedentary habits (ages range 15 to 43 years [mean 24 ± 7]) in whom no signs or symptoms of heart disease were found, including a normal electrocardiogram, and who denied any kind of illicit drug use. There were no significant differences between physiologic variables in the patient and control groups, except for blood pressure, which was lower in the study group (mean arterial pressure of 80 ± 9 vs 84 ± 8 mm Hg; p <0.02).

Echocardiographic and Doppler examinations: A complete M-mode, 2-dimensional echo and pulsed and color Doppler examination was performed by means of Aloka SSD-870 equipment (Aloka, Tokyo, Japan) using an ultrasound probe of 3.5 MHz for image purposes and 3.0 MHz for Doppler analysis.

The following points were considered from the M-mode and 2-dimensional studies: (1) dimensions of cardiac chambers according to established standards[8]; (2) left ventricular ejection fraction derived from M-mode systolic and diastolic diameters[9] — a simple accurate measure of systolic function when no segmental wall motion abnormalities or left ventricular dilatation are present,[10] (as was the case in all our subjects); and (3) detection of morphologic abnormalities of the valves — presence or absense of eventual abnormalities were assessed by the operator and, in all cases, the opinion of a second experienced observer unaware of the other's assessment was required; in case of disagreement, the opinion of a third observer was considered.

Color and pulsed Doppler flow examinations were performed at the level of the 4 heart valves considering (1) the presence or absence of valvular regurgitation and its quantitation[11,12]; (2) pulsed Doppler parameters of ventricular diastolic function — early diastolic mitral and tricuspid deceleration time and quotient between early and late maximal diastolic flow velocities (E/A ratio)[13]; and (3) pulmonary time-to-peak flow velocity as an indirect estimation of pulmonary artery resistance.[14] For all numeric Doppler parameters, the mean of ≥3 measurements taken at the end-expiratory period was considered.

Statistics: Results are expressed as mean ± standard deviation. A p value <0.05 was considered statistically significant. Unpaired Student's *t* test was used to compare numerical variables between patient and control groups. Chi-square and Fisher's exact tests were used to compare discrete clinical and echocardiographic variables between the 2 groups.

RESULTS

No significant differences were observed between the 2 groups regarding cardiac dimensions or left ventricular systole function.

The morphologic abnormalities of the valves that could be detected by echocardiography were: (1) mitral and tricuspid valvular focal thickening, defined as a small (<5 mm) echogenic protruding mass distorting the valve contour and eliciting a distinctive signal by M-mode examination (Figure 1) on an otherwise normal valve; and (2) mitral or tricuspid valve prolapse, diagnosed when a portion of any leaflet billowed in systole across the anular plane into the atrium (Figure 2) (this being visualized both in the parasternal long-axis and 4-chamber views.[15,16] Despite the mentioned abnormalities, a valve with mixomatous echocardiographic appearance was not observed in any subject. Moreover, focal thickening and prolapse never coincided in the same patient. No apparent abnormalities were observed at the aortic or pulmonary valves. Table I lists the distribution of these abnormalities among the 2 groups.

Doppler study of valve regurgitation showed a significantly higher prevalence of mitral, tricuspid and pulmonary insufficiency among patients in the study group (Table II). No aortic regurgitation was detected in either patients or control subjects. No higher prevalence or degree of severity of valvular regurgitation could be seen in addicted patients with valvular abnormalities compared with those exhibiting apparently normal valves.

Doppler data on diastolic ventricular function and pulmonary resistances are listed in Table III. Significant differences were found in mitral and tricuspid deceleration time; deceleration time was moderately increased in the study group.

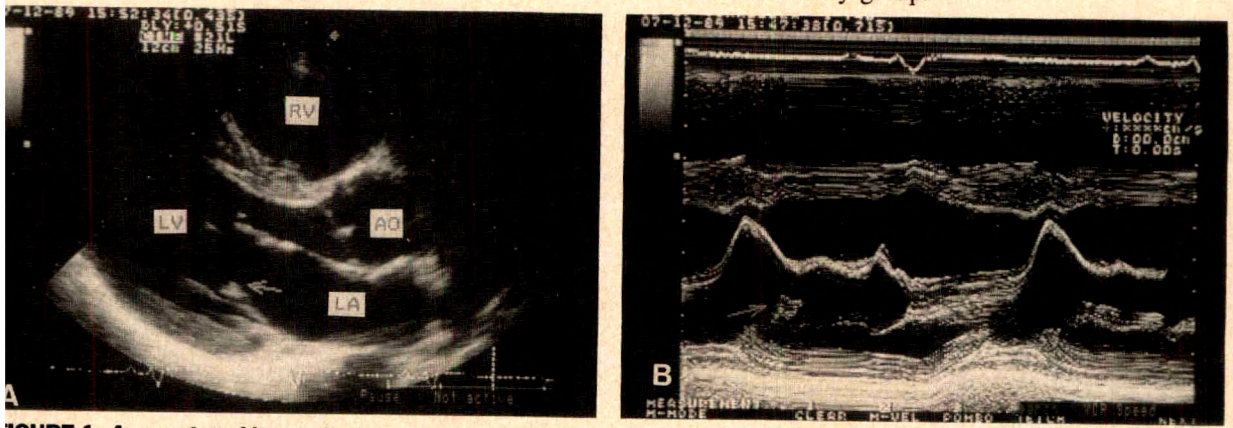


FIGURE 1. ***A,*** **parasternal long-axis view of the left heart chambers showing a focal thickening located at the edge of the posterior mitral valve leaflet** ***(arrow).*** ***B,*** **a 2-dimensional guided M-mode tracing helps to recognize as definitely abnormal the thickening of the posterior valve leaflet** ***(arrow).*** **Ao = aorta; LA = left atrium; LV = left ventricle; RV = right ventricle.**

TABLE I Valvular Abnormalities Detected by Two-Dimensional Echocardiography

	Pt. (no.)	Control	p Value
Mitral valve	6/68	1/41	NS
Prolapse	2	1	
Thickening	4	—	
Tricuspid valve	13/68	0/41	0.007
Prolapse	5	—	
Thickening	8	—	
Total	19/68	1/41	0.0009

NS = not significant.

TABLE II Prevalance of Valvular Regurgitations Detected and Quantified by Pulsed and Color Doppler

	Patients	Control	p Value
Mitral	19/68	6/41	0.08
Mild	16	4	
Moderate	3	2	
Tricuspid	47/68	20/41	0.02
Mild	36	19	
Moderate	11	1	
Pulmonary	27/68	9/41	0.04

TABLE III Estimation of Diastolic Ventricular Function and Pulmonary Vascular Resistances by Pulsed Doppler

	Patients	Control	p Value
Mitral flow			
Deceleration time (ms)	183 (45)	156 (28)	0.0001
Ratio E/A	1.8 (.5)	1.8 (.6)	NS
Tricuspid flow			
Deceleration time (ms)	179 (70)	157 (29)	0.027
Ratio E/A	1.7 (.4)	1.8 (.6)	NS
Pulmonary flow			
Time-to-peak (ms)	128 (18)	134 (21)	NS

E/A = early and late maximal diastolic flow velocities.

All the significantly abnormal findings in the group of drug addicts — morphologic valve abnormalities, presence of valvular regurgitation and Doppler parameters of diastolic function — were not related to the age of the subjects, time of addiction and the presence or absence of human immunodeficiency virus antibodies.

DISCUSSION

The results of our study reenforce the hypothesis that a prolonged intravenous drug habit may induce the presence of morphologic cardiac valve abnormalities demonstrated on echocardiography, without apparent signs or symptoms of heart disease. Two types of lesions could be defined: The first appears as a tiny focal thickening of either the mitral (Figure 1) or tricuspid valves. This lesion differs from a true valvular vegetation in its lack of a distinctive echogenic pattern and in its absence of inertial movements independent from cardiac valves on real-time echocardiographic examination.[17] There was disagreement between the first 2 observers in the assessment of such abnormalities in only 2 of 12 subjects, requiring the opinion of a third one. The second type of lesion was valve prolapse: There was a significantly higher prevalence of tricuspid valve prolapse (Figure 2) in the study group (7.3%) than in control subjects (0%), and in subjects reported in other series (0.1 to 5.5%).[16] An interpretation of the first lesion (valvular focal thickening) should alert one to the process of platelet-fibrin deposition following the endocardial inoculation of particles and claimed as the basis for an infectious endocarditis.[6] A potential causative relation between the drug habit and a valvular prolapse is a more intriguing hypothesis. However, considering that the histologic basis for a prolapse is the loss of rigid collagenous support of the valvular structure,[16] it is not presumptuous to regard this process as an alternative possible form of damage also due to the drug itself or to some of the many insoluble substances known to be present in the injected material.[5,6]

The presence of mild valvular regurgitation detected by Doppler imaging in normal persons is well known,[18] usually without a clearly audible murmur.[19] This was also confirmed in our control group (Table II); nevertheless, its prevalence was significantly increased in the study group, but not limited to those with echocardiographic valvular abnormalities. This fact argues in favor of a drug-induced valvular abnormality that, in some

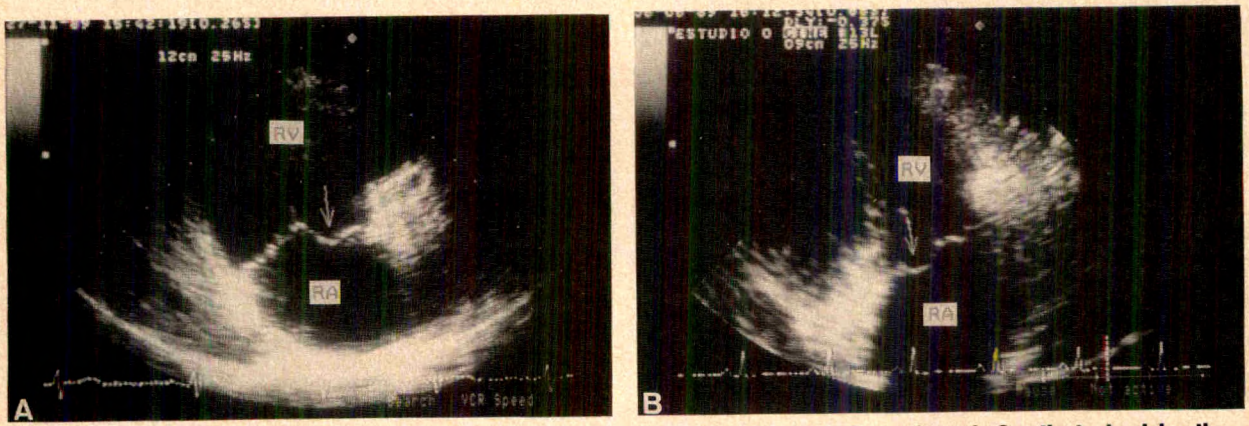


FIGURE 2. Parasternal long-axis view of the right heart chambers showing tricuspid valve prolapse in 2 patients, implying the anterior *(A)* and the posterior *(B)* leaflets. RA = right atrium; RV = right ventricle.

patients with Doppler regurgitations but without echocardiographic abnormalities, could be subtle enough not to be detected by echocardiography.

Statistically significant differences were observed in some of the Doppler indexes of diastolic function between patient and control groups (Table III). Nevertheless, a word of caution is needed before concluding that they reflect an actual impairment in ventricular relaxation in addicted patients. In addition to diastolic dysfunction, it has been shown[20] that a reduction in cardiac preload induces changes very similar to those observed in our study group: increasing mitral and tricuspid deceleration time of early diastolic flow. Provided that these patients were all receiving both propoxyphene and benzodiazepines, which are known to reduce arterial and venous resistances[21,22] (arterial blood pressure was significantly lower in addicted patients than in the control group), the mentioned Doppler abnormalities can be attributed to this fact.

In addition, as reported in previous studies,[23] the detection of human immunodeficiency virus antibodies could not be related to echocardiographic abnormal findings.

In conclusion, our results show a high prevalence of echocardiographic valvular abnormalities at the mitral and tricuspid valve levels in asymptomatic chronic intravenous heroin users. It seems acceptable to speculate that these lesions may constitute the grounds for a future infective endocarditis. On the other hand, no impairment in the structure and systolic or diastolic function of the heart can be evidenced in these patients.

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Differences in Myocardial Fluoro-18 2-Deoxyglucose Uptake in Young Versus Older Patients with Hypertrophic Cardiomyopathy

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The purpose of this study was to determine whether regional myocardial glucose use in patients diagnosed as having hypertrophic cardiomyopathy (HC) at a younger age differs from that in those diagnosed at middle to old age. Sixteen patients with HC (group 1 aged <40 years (n = 8); group 2 aged >40 (n = 8) were studied using positron emission tomography and fluoro-18 2-deoxyglucose (FDG). All patients were diagnosed as having HC within 6 years of the study. Contiguous regions of interest were selected circumferentially on each cross-sectional image of the left ventricular wall. In each region of interest, % FDG fractional uptake was calculated. In each patient, % left ventricular FDG fractional uptake was determined as a mean value of % FDG fractional uptake in each region of interest. Moreover, as a measure of nonhomogeneity, the % interregional coefficient of variation in FDG fractional uptake was calculated in each patient. Whereas % left ventricular FDG fractional uptake did not differ between the 2 groups, the % interregional coefficient of variation in FDG fractional uptake was increased in group 1 compared with that in group 2 (11.5 ± 3.6 vs 7.4 ± 1.6%; p <0.02). Interventricular septum/left ventricular posterior wall thickness ratio and total counts in cross-sectional image did not differ between the 2 groups. These data suggest that patients diagnosed as having HC at a younger age have more nonhomogeneous myocardial metabolic characteristics than do patients diagnosed at middle or old age, and support the notion that HC in the young may be different from that in the middle-aged or elderly.

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Hypertrophic cardiomyopathy (HC) is characterized by a hypertrophic ventricle without other cardiac or systemic disease known to cause ventricular hypertrophy.[1] Several investigators reported a difference in the clinical course between young and middle-aged or elderly patients with HC. McKenna et al[2] reported that patients diagnosed in childhood had a higher annual mortality rate than did those diagnosed between 45 and 60 years of age. Maron et al[3] demonstrated that 71% of the patients were aged <30 years at cardiac catastrophe. Koga et al[4] showed that sudden death occurred more often in the young. More recently, Lever et al[5] demonstrated differences in cardiac shape between young and elderly patients. Thus, these earlier studies show that HC in the young is different from that in the middle-aged or elderly with regard to prognosis and morphology. However, there is no study concerning whether myocardial metabolic characteristics differ between these age groups. This study investigates whether or not regional myocardial glucose uptake differs between younger and middle-aged to elderly patients. We studied 2 age groups of patients with HC (< and >40 years) using positron emission tomography and a glucose analog fluoro-18 2-deoxyglucose (FDG).

METHODS

Study patients: The study group was comprised of 16 consecutive patients with HC (aged 13 to 77 years) referred to our hospital. The diagnosis of HC was based on 2-dimensional echocardiographic demonstration of a hypertrophied, nondilated left ventricle in the absence of other cardiac or systemic disease known to cause left ventricular hypertrophy.[1] All patients were diagnosed as having HC within 6 years of the positron emission tomography study. We divided the patients in 2 groups according to age (group 1 aged <40 years; group 2 aged >40). The main clinical features of the patients are listed in Tables I and II. No patient had diabetes mellitus. The purpose and nature of this study were approved by the committee for administration of radioactive substance of the Tohoku University School of Medicine. Informed consent was obtained from all patients before each study.

Echocardiography and cardiac catheterization: M-mode and 2-dimensional echocardiography were performed in all 16 patients on the day of the tomographic study (SSH-65A, Toshiba, Tokyo, Japan). Cardiac catheterization was performed within 4 months of the

TABLE I Clinical and Positron Emission Tomographic Data from Patients with Hypertrophic Cardiomyopathy in Group 1

			Echocardiographic Findings					PET Data	
Patient	Age (yr) & Sex	NYHA Class	IVS Thickness (mm)	LVPW Thickness (mm)	IVS/LVPW	Fractional Shortening	PG (mmHg)	% LV FDG Fractional Uptake	% Interregional Coefficient of Variation
1	13M	II	17	12	1.4	0.51	—	6.5	11.5
2	16F	II	16	11	1.5	0.51	45	4.9	10.8
3	19F	III	19	11	1.7	0.34	15	5.4	8.7
4	23M	I	17	10	1.7	0.50	0	9.2	16.2
5	28M	I	20	15	1.3	0.47	0	3.0	17.3
6	33M	I	16	9	1.8	0.44	0	4.0	11.5
7	36M	I	16	11	1.5	0.40	30	5.0	8.1
8	39M	I	21	10	2.1	0.35	—	5.6	7.7
Mean ± SD	26 ± 10		18 ± 2	11 ± 2	1.6 ± 0.3	0.44 ± 0.07	15 ± 19	5.4 ± 1.9	11.5 ± 3.6

FDG = fluoro-18 2-deoxyglucose; IVS = interventricular septum; LV = left ventricular; LVPW = left ventricular posterior wall; NYHA Class = New York Heart Association functional class; PET = positron emission tomographic; PG = left ventricular outflow tract pressure gradient measured by cardiac catheterization; — = not measured.

TABLE II Clinical and Positron Emission Tomographic Data from Patients with Hypertrophic Cardiomyopathy in Group 2

			Echocardiographic Findings					PET Data	
Patient	Age (yr) & Sex	NYHA Class	IVS Thickness (mm)	LVPW Thickness (mm)	IVS/LVPW	Fractional Shortening	PG (mm Hg)	% LV FDG Fractional Uptake	% Interregional Coefficient of Variation
9	46M	I	17	12	1.4	0.32	—	5.7	9.5
10	49M	II	22	14	1.6	0.43	50	4.4	8.2
11	53M	II	21	16	1.3	0.36	0	4.3	8.3
12	55M	I	18	11	1.6	0.43	0	6.5	6.5
13	55M	II	18	13	1.4	0.38	0	6.0	9.3
14	55M	III	19	11	1.7	0.58	0	5.0	6.1
15	61M	I	20	12	1.7	0.38	80	5.8	5.9
16	77F	II	17	12	1.4	0.32	—	7.3	5.4
Mean ± SD	56 ± 9		19 ± 2	13 ± 2	1.5 ± 0.2	0.40 ± 0.08	22 ± 35	5.6 ± 1.1	7.4 ± 1.6

Abbreviations as in Table I.

positron emission tomographic study in 12 patients (6 in each group).

Radiopharmaceutical and scanning procedure: We used the glucose analog FDG to assess regional myocardial glucose uptake. FDG competes with glucose for membrane transport sites and hexokinase. However, the end product FDG-6-phosphate is not further metabolized and trapped within the cell.[6,7] FDG used in this study was synthesized using a fully automated synthesis system.[8]

We used a single-slice positron tomograph (ECAT II, CTI, Knoxville, Tennessee) with a spacial resolution of 17 mm full-width at half maximum in the transverse plane and a slice thickness of 17 mm full-width at half maximum. Calibration between a well counter used for measuring plasma radioactivity and the positron tomograph was performed weekly. Each patient was positioned within the positron scanner 3 to 4 hours after a carbohydrate-rich meal. Medications (β blockers or calcium antagonists) were not discontinued before the study. A transmission scan was performed using a 2 mCi germanium-68/gallium-68 ring source for the attenuation correction. After an arterial blood sample was obtained from a catheter placed in the dorsalis pedis or radial artery to determine the plasma concentrations of glucose, insulin and free fatty acids, 4 to 8 mCi of FDG dissolved in 6 ml of 0.9% sodium chloride solution was infused intravenously for 1 minute. We acquired 4 cross-sectional images of the left ventricle at 10 mm intervals by scanning over a period of 300 seconds per plane, 45 to 65 minutes after the FDG injection. Serial arterial blood samples were withdrawn until the end of scanning (every 20 seconds up to 180 seconds, and then 4, 5, 7, 10, 15, 20, 30, 45 and 65 minutes after the FDG injection).

Data analysis: The FDG scans were corrected for decay and attenuation. We analyzed only 1 cross-sectional image through the mid-left ventricle in each patient. Contiguous 0.73 cm^2 (9 pixels) rectangular regions of interest were selected circumferentially along the left ventricular wall. Number of regions of interest varied (from 11 to 19) with left ventricular size. Percent FDG fractional uptake in each region of interest was calculated as described by Camici et al[9]: % FDG fractional uptake in region of interest = $(C_{M\ (FDG)}/\int_0^T C_{P\ (FDG)}dt) \times 100$, where $C_{M\ (FDG)}$ is the FDG radioactivity per pixel in each region of interest in the myocardium, and $\int_0^T C_{P\ (FDG)}dt$ is the integral of the plasma FDG radioactivity per gram from the time of the injection to the end of scanning. In each patient, we calculated % left ventricular FDG fractional uptake as the mean % FDG fractional uptake in each region of interest. Furthermore, as a measure of nonhomogeneity, % interregional coefficient of variation (SD/mean × 100)

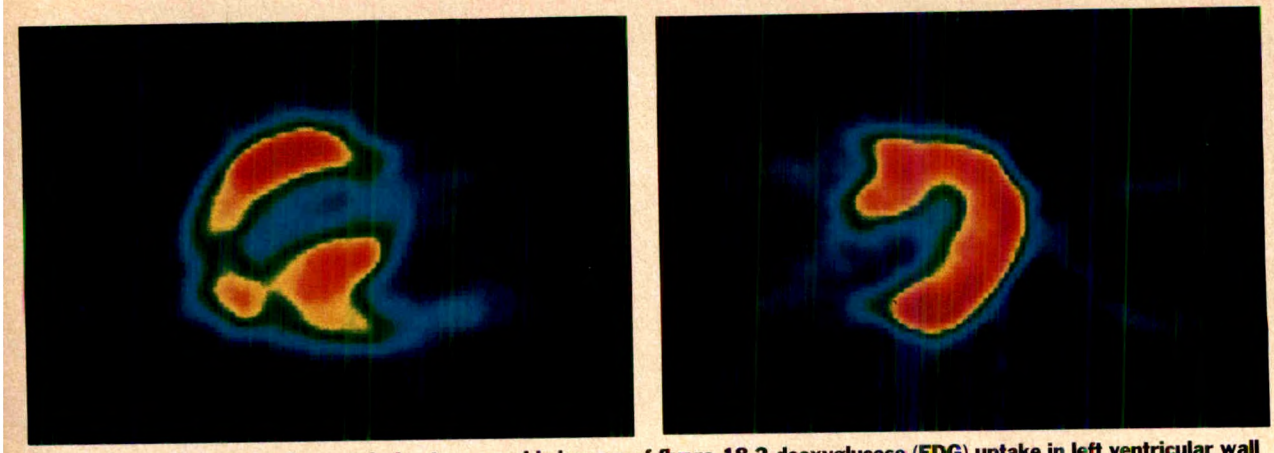


FIGURE 1. Transaxial positron emission tomographic images of fluoro-18 2-deoxyglucose (FDG) uptake in left ventricular wall of patients 5 *(left)* and 15 *(right)*. In each cross-sectional image, interventricular septum is at *upper left*, anterior wall is at *right*, and lateral wall is at *lower right*. FDG uptake is more nonhomogeneous in patient 5 than in 15.

of % FDG fractional uptake in the region of interest was determined in each patient.[10]

Plasma glucose concentration was determined by a modification[11] of the glucose oxidase method,[12] plasma insulin concentration was measured by radioimmunoassay,[13] and the plasma concentration of free fatty acids was determined by an enzymatic method.[14]

Data are presented as mean ± SD. The unpaired Student's *t* test was used to compare the parameters between the 2 groups of patients. A p value <0.05 was considered significant.

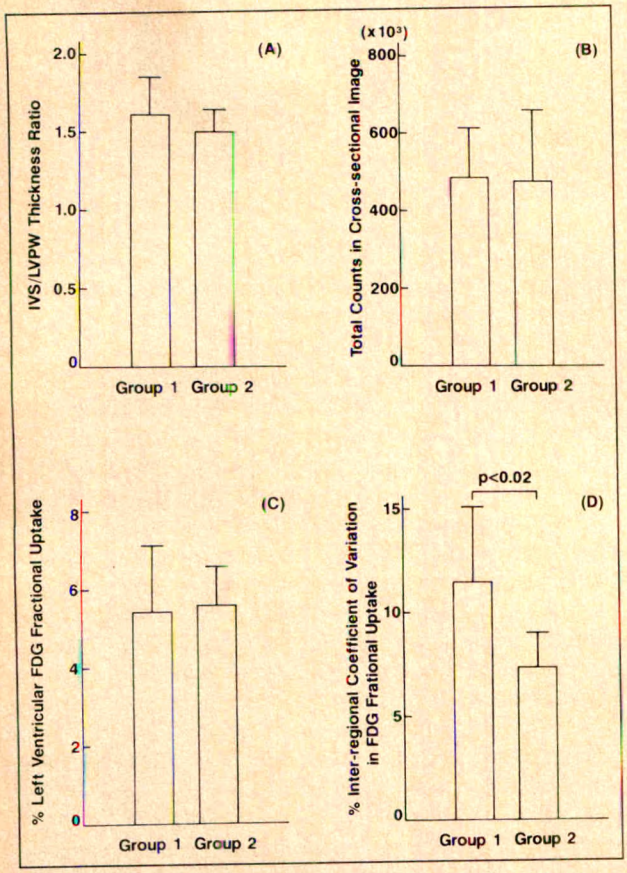


FIGURE 2. Graphs showing thickness ratios between interventricular septum (IVS) and left ventricular posterior wall (LVPW) *(A)*, total counts in each cross-sectional image *(B)*, % left ventricular fluoro-18 2-deoxyglucose (FDG) fractional uptake *(C)*, and % interregional coefficient of variation in FDG fractional uptake *(D)* in groups 1 and 2. Values are mean ± SD.

RESULTS

Echocardiography and cardiac catheterization: Echocardiographic data are listed in Tables I (group 1) and II (group 2). The thicknesses of the interventricular septum and the left ventricular posterior wall, and the interventricular septum/left ventricular posterior wall thickness ratio (Figure 2A) did not differ between the 2 groups. Left ventricular fractional shortening was normal in all patients and did not differ between groups 1 and 2. Left ventricular outflow tract pressure gradient measured by cardiac catheterization did not differ between the 2 groups. Coronary angiography showed no significant % diameter stenosis (>50%) in either group.

Plasma concentration of glucose, insulin, and free fatty acids: The plasma concentrations of glucose (116 ± 17 in group 1 vs 135 ± 30 mg/dl in group 2), insulin (18.6 ± 14.6 in group 1 vs 28.3 ± 26.9 μIU/ml in group 2) and free fatty acids (1.14 ± 1.21 in group 1 vs 0.84 ± 0.82 mEq/liter in group 2) immediately before the FDG injection did not differ between the 2 groups.

Myocardial fluoro-18 2-deoxyglucose uptake: Figure 1 shows representative positron emission tomographic images of patients in groups 1 and 2. Total counts in each cross-sectional image were 485,000 ± 138,000 in group 1, and 477,000 ± 194,000 in group 2, and did not differ between the 2 groups (Figure 2B). The % left ventricular FDG fractional uptake and the % interregional coefficient of variation in FDG fractional uptake of each patient are listed in Tables I and II. The % left ventricular FDG fractional uptake did not differ between the 2 groups (Figure 2C). The % interregional coefficient of variation in FDG fractional uptake was increased in group 1 compared with that in group 2 (Figure 2D).

The % interregional coefficient of variation in FDG fractional uptake did not differ between patients treated with β blockers and those treated with calcium antagonists (10.4 ± 3.4 vs 9.5 ± 3.4%, respectively).

DISCUSSION

We demonstrated that left ventricular FDG uptake is more nonhomogeneous in younger patients with HC than that in middle-aged to elderly patients. We also found that the increased nonhomogeneity in uptake was not associated with increased nonhomogeneity in left ventricular wall thickness, decreased total counts in cross-sectional image, or decreased % left ventricular FDG fractional uptake. It is unlikely that the nonhomogeneous FDG uptake in the younger patients changes to a more homogeneous one as the patient ages, because all patients in our study were diagnosed as having HC within 6 years of the positron emission tomographic study. Therefore, it is more likely that patients diagnosed at a younger age have more nonhomogeneous myocardial FDG uptake than do those diagnosed at middle or old age.

Methodologic considerations: We did not study an age-matched control group. However, in our preliminary study, 7 normal subjects were examined using positron emission tomography and FDG, and no correlation was found between the % interregional coefficient of variation in FDG fractional uptake and age. Therefore, it is unlikely that normal young people without HC also demonstrate more nonhomogeneous myocardial glucose uptake than do normal old people.

We did not correct regional myocardial FDG concentration for regional wall thickness. The relation between the apparent isotope concentration in an image and the true concentration depends on object size.[15] However, it is unlikely that the difference in the % interregional coefficient of variation in FDG fractional uptake between the 2 age groups is caused by the difference in the degree of nonhomogeneity of regional wall thickness, because the degree of asymmetrical septal hypertrophy did not differ between the 2 groups.

Increased nonhomogeneity of glucose use in younger patients: The mechanism of increased nonhomogeneity of myocardial glucose use is unclear. Glucose use is accelerated in myocardial ischemia.[9,16] Several studies suggested that myocardial ischemia plays an important role in the pathophysiology of HC. Pasternac et al[17] and Cannon et al[18] demonstrated hemodynamic and metabolic evidence of pacing-induced myocardial ischemia in patients with HC. O'gara et al[19] found an exercise-induced myocardial perfusion abnormality in patients with this disorder. However, Grover-McKay et al[20] reported that mildly symptomatic patients with HC had no evidence of myocardial ischemia at rest using positron emission tomography, FDG, carbon-11-labeled palmitate and nitrogen-13-labeled ammonia. Further investigation, including myocardial perfusion study, is needed to determine whether nonhomogeneity of myocardial FDG uptake is caused by regional myocardial ischemia.

Widespread myocardial fibrosis or scarring was reported in patients with HC.[21–23] These histologic changes may influence the distribution of regional myocardial FDG uptake. Therefore, increased nonhomogeneity in FDG uptake may be caused by increased heterogeneity in the amount of myocardial fibrosis or scarring in younger patients.

Free fatty acids inhibit myocardial glucose metabolism.[24] First, interstitial lipid deposition may be more nonhomogeneous in younger patients. Although the plasma concentration of free fatty acids did not differ between the 2 groups, the interstitial free fatty acid concentration may be more nonhomogeneous in younger patients and cause more nonhomogeneous exogenous glucose uptake. Second, Merhige et al[25] reported that catecholamine infusion suppressed myocardial glucose metabolism in the normal canine myocardium, probably due to increased myocardial free fatty acid use. Therefore, nonhomogeneity of myocardial glucose uptake may be caused by more nonhomogeneous regional sympathetic discharge or catecholamine receptor activities.

Several investigators reported that young patients with HC have a different clinical course or cardiac shape from that of middle-aged or elderly patients.[2–5] We showed that the % interregional coefficient of variation in FDG fractional uptake was increased in younger patients compared with that in middle-aged to elderly patients. Interventricular septum/left ventricular posterior wall thickness ratio, total counts in cross-sectional image, and % left ventricular FDG fractional uptake did not differ between the 2 groups and could not explain the difference in nonhomogeneity of FDG uptake. The difference in nonhomogeneity is not due to the difference in the plasma concentration of glucose, insulin and free fatty acids, because these 3 factors did not differ between the 2 groups. Although further studies are needed to understand the mechanisms involved, our data suggest that patients diagnosed with HC at a younger age have more nonhomogeneous myocardial metabolic characteristics than do patients diagnosed at middle or old age, and support the notion that HC in the young may be different from that in the middle-aged or elderly.

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Cholinergic Baroreflex Vasodilatation: Defect in Heart Transplant Recipients Due to Denervation of the Ventricular Baroreceptor

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Afferent denervation of the ventricular baroreceptor may impair reflex vasodilatation after heart transplantation. This may alter the regulation of blood pressure and contribute to arterial hypertension. A baroreceptor-loading procedure was performed in 23 heart transplant recipients with cyclosporine A immunosuppression and 11 control subjects using a continuous infusion of increasing doses of angiotensin II (15 and 30 ng/kg · min). After m-cholinoceptor blockade the procedure was repeated in order to study the contribution of cholinergic effects on vasodilatation in humans. Instantaneous vascular resistance was calculated as the ratio of mean blood pressure to stroke volume as evaluated by echocardiography.

When heart transplant recipients were compared with control subjects, infusion of 30 ng/kg · min of angiotensin II resulted in an increase in mean blood pressure of 43 ± 20 vs 31 ± 13 mm Hg ($p < 0.05$) and an increase in instantaneous resistance of 1.21 ± 0.61 vs 0.65 ± 0.38 mm Hg/ml ($p < 0.01$), respectively. M-cholinoceptor blockade with atropine (0.015 mg/kg) did not produce any change in blood pressure or resistance response to angiotensin II in heart transplant recipients. However, m-cholinoceptor blockade resulted in a significantly increased blood pressure and resistance response to angiotensin II in control subjects, which was similar to the response in heart transplant recipients to angiotensin II alone: The increase in mean blood pressure during administration of 30 ng/kg · min angiotensin II amounted to 47 ± 11 mm Hg, and the increase in instantaneous resistance to 1.13 ± 0.48 mm Hg/ml (for both, $p < 0.001$ vs control subjects without atropine; p = not significant vs heart transplant recipients). Thus, in humans, a potent cholinergic vasodilator baroreflex is present, originating exclusively from the ventricular baroreceptor. Cholinergic vasodilatation is absent after heart transplantation because of ventricular denervation. Thus, cardiac denervation considerably impairs control of blood pressure and is likely to be a causal factor for heart transplantation-associated arterial hypertension.

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Arterial hypertension is a serious consequence of heart transplantation. It is caused by an increase in systemic vascular resistance.[1,2] Heart transplantation is accompanied by afferent denervation of the ventricular baroreceptor, whereas the arterial baroreceptors remain innervated and reveal normal function.[3–5] It is not clear whether denervation of the heart modulates the regulation of blood pressure and plays a role in the development of transplantation-associated hypertension. Several studies presume a potential neurally mediated cause for the hitherto unexplained aggravation of cyclosporine-induced arterial hypertension in heart transplant recipients.[2,3] This may be due to an impaired baroreflex modulation of vascular tone. In experimental animals, afferent ventricular denervation results in an increase in sympathetic adrenergic nerve activity and vascular resistance, with a subsequent elevation in blood pressure.[6,7] Furthermore, the relative contributions of withdrawal of sympathetic adrenergic tone (i.e., passive vasodilatation) and activity of the cholinergic sympathetic vasodilator pathway (i.e., active vasodilatation) to control of blood pressure are not established in humans.[8] Studies in experimental animals indicate a potential role of m-cholinoceptor-mediated baroreflex modulation of vascular tone.[9,10] Moreover, a cholinergic chemoreflex vasodilatation originating from ventricular chemoreceptor endings has been demonstrated in experimental animals and humans.[11,12] In an analogy to these observations it is not unreasonable to hypothesize that cholinergic vasodilatation may be mediated by the ventricular baroreceptor.

METHODS

Twenty-three consecutive heart transplant recipients (22 men and 1 woman, mean age 46 ± 9 years) were investigated 3.4 ± 1.6 years after orthotopic heart transplantation. All patients were without a history or clinical signs of heart failure. Echocardiography was normal in each patient. Acute rejection was excluded by endomyocardial biopsy specimens within 24 hours after the investigation in each patient. Immunosuppressive therapy consisted of 272 ± 61 mg/day of cyclosporine A (n = 23), 6.7 ± 1.2 mg/day of prednisone (n = 21)

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TABLE I Hemodynamic Effects in Controls, Atropine-Pretreated Controls and Heart Transplant Recipients

	SAP (mm Hg)	MAP (mm Hg)	DAP (mm Hg)	HR (min^{-1})	EDV (ml)	ESV (ml)	SV (ml)	EF (%)	IR (mm Hg/ml)	ΔSAP/ΔESV (mm Hg/ml)
Controls										
Rest	120 ± 11	90 ± 9	75 ± 9	71 ± 11	108 ± 18	35 ± 10	73 ± 12	68 ± 7	1.26 ± 0.18	
Angiotensin 15	135 ± 81++	103 ± 14++	86 ± 14+	64 ± 10++	109 ± 19	40 ± 11+	69 ± 12+	64 ± 6++	1.54 ± 0.36++	3.28 ± 1.2
Angiotensin 30	157 ± 17++	121 ± 13++	104 ± 11++	60 ± 10++	111 ± 18	45 ± 11++	66 ± 12++	59 ± 6+++	1.91 ± 0.42+++	
Controls, atropine										
Rest	116 ± 13	88 ± 12	74 ± 11	67 ± 8	103 ± 20	34 ± 9	69 ± 13	67 ± 5	1.20 ± 0.41	
Atropine	115 ± 11	89 ± 9	77 ± 10	93 ± 12***	98 ± 20	32 ± 10	66 ± 14	68 ± 7	1.40 ± 0.31	
Angiotensin 15	141 ± 16++	113 ± 13++	99 ± 13*++	84 ± 12***+	100 ± 21	40 ± 11++	60 ± 13++	61 ± 6+++	1.96 ± 44*++	3.35 ± 1.0
Angiotensin 30	170 ± 20++	136 ± 16*++	119 ± 16*++	84 ± 14***+	106 ± 23+	50 ± 13++	57 ± 13++	54 ± 6+++	2.53 ± 0.74*+++	
Heat transplant recipients										
Rest	128 ± 14#	99 ± 13*#	84 ± 13*#	91 ± 16**###	86 ± 20**	31 ± 12	55 ± 13**#	64 ± 9	1.90 ± 0.6**#	
Angiotensin 15	159 ± 10***##	125 ± 8***#+++	107 ± 9***#+++	89 ± 25***	93 ± 26+	43 ± 16+++	53 ± 13**	55 ± 11*+++	2.51 ± 0.8***#+++	3.05 ± 1.3
Angiotensin 30	182 ± 15***+++	142 ± 12***+++	125 ± 15***+++	93 ± 17***	99 ± 24+	53 ± 18+++	49 ± 11**++	48 ± 10*+++	3.08 ± 0.8***+++	

*, **, *** $p < 0.05$, < 0.01, < 0.001 Controls, atropine versus controls and heart transplant recipients versus controls.
#, ##, ### $p < 0.05$, < 0.01, < 0.001 heart transplant recipients versus Controls, atropine.
+, ++, +++ $p < 0.05$, < 0.01, < 0.001 angiotensin 15 or angiotensin 30 versus rest or atropine, respectively.
Systolic, mean and diastolic arterial blood pressures (SAP, MAP, DAP), heart rate (HR), end-diastolic, end-systolic and stoke volumes (EDV, ESV, SV), ejection fraction (EF) and instantaneous resistance (IR [i.e., the ratio of MAP to SVI]) in controls (n = 11), atropine pretreated controls (n = 11) and heart transplant recipients (n = 23) at rest or after atropine, respectively, and during 15 and 30 ng/kg · min of angiotensin II, respectively (angiotensin 15, angiotensin 30). The contractility index is calculated as the slope between the relations of systolic arterial pressure to end-systolic volume at rest and during angiotensin II (30 ng/kg · min) (Δ SAP/Δ ESV).

and 53 ± 15 mg/day of azathioprine (n = 9). Twenty-two patients received antihypertensive drugs: 10.8 ± 5.0 mg/day of enalapril (n = 16), 218 ± 99 mg/day of verapamil (n = 10) and 46 ± 22 mg/day of furosemide (n = 14). Antihypertensive therapy was withdrawn 24 to 36 hours before the investigation. An additional 4 patients were excluded from the study because of systolic blood pressure values >160 mm Hg at rest after cessation of antihypertensive therapy. The control group consisted of 11 healthy, nonsmoking male control subjects without any medication. Mean age was 41 ± 7 years and did not differ significantly from the age of the heart transplant recipients.

The control of vascular tone by different baroreflexes is variable in different vascular beds,[7,8,12] and the localization of the most pronounced effects of cholinergic vasodilatation in humans is not established.[7,8,12,13] Therefore, an experimental design evaluating circulation in general is preferable. Systolic and diastolic blood pressures were measured in the right arm with an automated sphygmomanometer (Datascope Accutorr, Datascope, Bremen, Germany). Mean arterial pressure was calculated as diastolic pressure plus one-third of pulse pressure. Heart rate was obtained from simultaneous electrocardiographic recordings. Two-dimensionally guided M-mode echocardiography in a short-axis view was performed using commercially available phased-array equipment with a 2.5 MHz transducer (Toshiba SSH 65-A). All recordings were obtained by the same investigator and evaluated independently by 2 principal investigators of the echocardiography department. Interobserver variability did not exceed 4.6%. Left ventricular end-systolic and end-diastolic diameter and fractional shortening were measured according to standard guidelines as the mean value of 5 cardiac cycles.[14] End-diastolic and end-systolic volumes, and stroke volume and ejection fraction were calculated using the Teichholz formula.[15] As an index of contractility, the linear slope between the relations of systolic blood pressure to end-systolic volume at rest and during therapy with angiotensin II was calculated as the difference in systolic pressure divided by the difference in end-systolic volume from baseline to maximum afterload stress.[16,17] As an index of vascular resistance the instantaneous resistance was calculated as the ratio of mean blood pressure to stroke volume.[18]

Study protocol: A cannula was inserted into the left antecubital vein. After 15 minutes of rest in the supine position, a continuous intravenous infusion of increasing doses of angiotensin II (Hypertensin®, Geigy) (15 ng/kg · min) was begun for 6 minutes, followed by 30 ng/kg · min for an additional 6 minutes. Measurements were obtained before the start of the infusion, at 6 and 12 minutes. After discontinuation of the infusion, heart rate and blood pressure returned to baseline values in <10 minutes. Twenty minutes after return to baseline values, a bolus injection of 0.015 mg/kg atropine sulfate was administered intravenously. Three minutes after application of atropine, angiotensin II was begun again as a continuous infusion as before. Atropine pretreatment was performed in all control subjects and in 11 consecutive heart transplant recipients.

TABLE II Hemodynamic Effects in Heart Transplant Recipients and Heart Transplant Recipients Pretreated with Atropine

	SAP mm Hg	MAP mm Hg	DAP mm Hg	HR (min^{-1})	EDV (ml)	ESV (ml)	SV (ml)	EF (%)	IR (mm Hg/ml)
Heart transplant recipients									
Rest	131 ± 13	100 ± 10	85 ± 11	92 ± 14	88 ± 24	29 ± 10	59 ± 17	66 ± 8	1.91 ± 0.78
Angiotensin 15	161 ± 12++	124 ± 10++	106 ± 10++	91 ± 13	94 ± 22	36 ± 11+	58 ± 16	61 ± 7++	2.30 ± 0.66++
Angiotensin 30	184 ± 15++	144 ± 11++	124 ± 13++	92 ± 17	96 ± 24+	47 ± 14++	49 ± 16+	51 ± 8++	3.13 ± 1.12+++
Heart transplant recipients, atropine									
Rest	130 ± 16	99 ± 9	84 ± 8	93 ± 12	87 ± 20	26 ± 10	60 ± 14	69 ± 8	1.79 ± 0.62
Atropine	131 ± 14	100 ± 9	84 ± 8	94 ± 14	85 ± 18	26 ± 9	59 ± 15	68 ± 10	2.03 ± 1.04
Angiotensin 15	160 ± 13++	124 ± 10++	105 ± 11++	90 ± 14	88 ± 19	32 ± 10+	56 ± 13	63 ± 8++	2.40 ± 0.93++
Angiotensin 30	184 ± 16++	145 ± 5++	126 ± 7++	90 ± 14	97 ± 19+	44 ± 12++	53 ± 12+	54 ± 7++	2.88 ± 0.90+++

+, ++, +++ = $p < 0.05$, < 0.01, < 0.001; angiotensin 15 or angiotensin 30 versus rest or atropine, respectively.
Significant differences between the 2 groups are not present.
Systolic, mean and diastolic arterial blood pressure (SAP, MAP, DAP), heart rate (HR), end-diastolic, end-systolic and stroke volumes (EDV, ESV, SV), ejection fraction (EF) and instantaneous resistance (IR [i.e., the ratio of MAP to SV]) in heart transplant recipients (n = 11) and atropine-pretreated heart transplant recipients (n = 11) at rest or after atropine, respectively, and during 15 and 30 ng/kg · min of angiotensin II, respectively (angiotensin 15, angiotensin 30).

TABLE III Increases in Blood Pressure and in Resistance in Controls and Heart Transplant Recipients Before and After m-Cholinoceptor Blockade

	Angiotensin II (15 ng/kg · min)				Angiotensin II (30 ng/kg · min)			
	Δ SAP (mm Hg)	Δ MAP (mm Hg)	Δ DAP (mm Hg)	Δ IR (mm Hg/ml)	Δ SAP (mm Hg)	Δ MAP (mm Hg)	Δ DAP (mm Hg)	Δ IR (mm Hg/ml)
Controls	16 ± 11	12 ± 10	11 ± 10	0.28 ± 0.25	37 ± 11	31 ± 13	28 ± 14	0.65 ± 0.38
Controls, atropine	26 ± 11*	24 ± 8**	22 ± 8**	0.55 ± 0.20**	55 ± 13**	47 ± 11**	42 ± 11**	1.13 ± 0.48**
Heart transplant recipients	30 ± 15**	26 ± 15**	24 ± 18**	0.64 ± 0.61*	54 ± 15**	43 ± 20*	41 ± 21*	1.21 ± 0.61**
Heart transplant recipients-II	30 ± 13	24 ± 11	21 ± 12	0.40 ± 0.33	53 ± 12	44 ± 10	39 ± 13	1.22 ± 0.41
Heart transplant recipients-II, atropine	29 ± 13	24 ± 9	21 ± 8	0.38 ± 0.22	52 ± 15	45 ± 10	41 ± 12	0.86 ± 0.48

* $p < 0.05$, ** $p < 0.01$ Controls, atropine versus controls and heart transplant recipients versus controls.
Increase in systolic, mean and diastolic arterial blood pressures (Δ SAP, Δ MAP, Δ DAP) and increase in instantaneous resistance (Δ IR) during infusion of 15 and 30 ng/kg · min of angiotensin II in controls (n = 11), atropine-pretreated controls (n = 11) and heart transplant recipients (n = 23). In a subgroup of heart transplant recipients (n = 11), application of atropine was performed (heart transplant recipients-II-atropine) and compared with the increase in blood pressure without m-cholinoceptor blockade (heart transplant recipients-II).
Differences between heart transplant recipients and atropine-pretreated controls and differences between heart transplant recipients-II and heart transplant recipients-II pretreated with atropine are not significant.
Other abbreviations in Tables I and II.

This study was performed in accordance with the declaration of Helsinki. Each control subject and heart transplant recipient gave informed consent.

Statistical analysis: Student's *t* test for paired or unpaired data, as appropriate, was performed to compare 2 means. The response to angiotensin II before and after application of atropine in control subjects and heart transplant recipients was compared by analysis of variance for repeated measures. All calculated p values were 2-tailed. All p values <0.05 were considered significant. All group data are given as mean ± standard deviation.

RESULTS

Blood pressure and vascular resistance: Effects of intravenous infusion of angiotensin II before and after m-cholinoceptor blockade on systolic, mean and diastolic blood pressures, heart rate, end-diastolic and stroke volumes, and ejection fraction and instantaneous resistance are listed in Tables I and II. Systolic, mean and diastolic blood pressures as well as instantaneous resistance at rest were higher in heart transplant recipients than in control subjects. During therapy with 15 and 30 ng/kg · min of angiotensin II, blood pressure and resistance increased significantly compared with baseline values in both heart transplant recipients and control subjects. Significant differences in systolic, mean and diastolic blood pressures and instantaneous resistance were present in heart transplant recipients versus control subjects at both angiotensin II dosages. The increase in systolic, mean and diastolic blood pressures and the increase in resistance induced by both angiotensin II dosages were significantly higher in heart transplant recipients than in control subjects (Table III and Figure 1).

Atropine pretreatment in control subjects did not change baseline values of blood pressure and resistance. The increase in systolic, mean and diastolic blood pressures and in resistance at both dosages of angiotensin II were significantly higher in atropine-pretreated than in untreated control subjects (Table III and Figure 1). Atropine pretreatment in heart transplant recipients affected neither blood pressure nor resistance at rest, nor the response of blood pressure and resistance to angiotensin II (Table II). The increase in systolic, mean and diastolic blood pressures and in resistance in atropine-pretreated heart transplant recipients did not differ from values without m-cholinoceptor blockade (Table III and Figure 2). The increases differed significantly in control subjects after m-cholinoceptor blockade and in heart transplant recipients compared with control subjects without m-cholinoceptor blockade at both angiotensin II levels. However, such increases were similar in control subjects after m-cholinoceptor blockade and in

heart transplant recipients at both angiotensin II levels (Table III and Figure 1).

Left ventricular dimensions and contractility: End-diastolic volumes were significantly smaller in heart transplant recipients than in control subjects, resulting in a significantly smaller stroke volume (Table I). Ejection fractions were similar (64 ± 9 vs 68 ± 7%). During pressure increase, significant changes were observed for end-systolic volume, stroke volume and ejection fraction in both heart transplant recipients and controls. Contractility indexes were similar in controls, controls after m-cholinoceptor blockade and heart transplant recipients (Table I). Thus, potential baroreflex-mediated contractility changes in the innervated control hearts during pressure increase are absent.

Heart rate: Heart rate of the denervated heart at rest was significantly higher. During pressure increase, a significant decrease in heart rate occurred in controls. After m-cholinoceptor blockade, a smaller but still significant heart rate decrease during pressure increase was observed in controls. In heart transplant recipients with and without m-cholinoceptor blockade no significant changes in heart rate were detected during pressure increase. Heart rate in controls after m-cholinoceptor blockade and in heart transplant recipients at rest were similar (93 ± 12 vs 91 ± 16 beats/min), and the differences in heart rate during pressure increase were not significant.

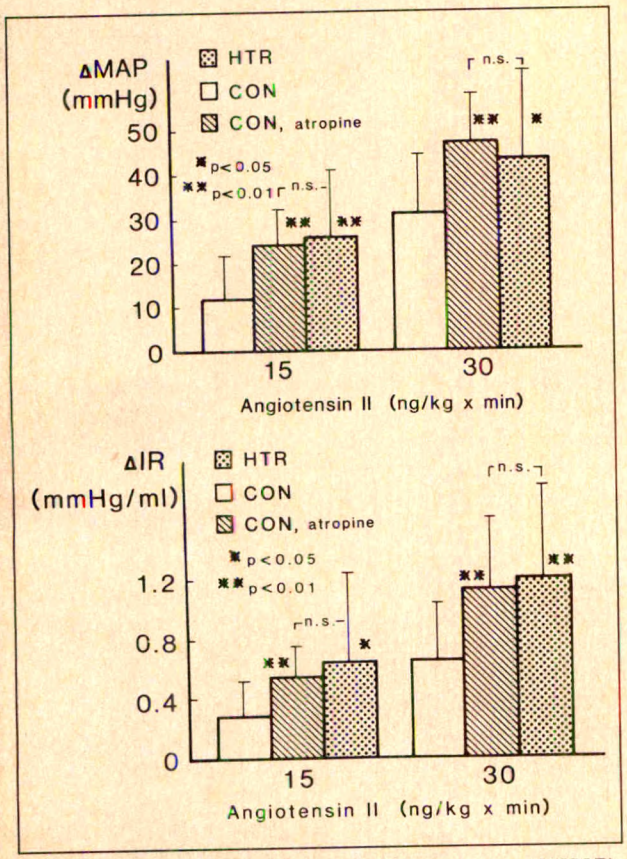


FIGURE 1. Increases in mean arterial blood pressure (ΔMAP), instantaneous resistance (ΔIR) in controls (CON, n = 11), atropine pretreated controls (CON, atropine, n = 11), and in heart transplant recipients (HTR, n = 23) during infusion of 15 and 30 ng/kg · min of angiotensin II. Increase in blood pressure and resistance is significantly augmented in heart transplant recipients and atropine-pretreated controls compared with untreated controls. However, increases in blood pressure and in resistance in heart transplant recipients and atropine-pretreated controls is nearly identical. n.s. = not significant.

DISCUSSION

Cholinergic baroreflex vasodilatation in healthy subjects: The physiologic role of the sympathetic cholinergic vasodilator pathway,[8,12,19] which may act by preganglionic inhibition of norepinephrine release and by stimulation of m-cholinoceptors on the vascular smooth muscle cell,[20] in baroreflex-mediated vasodilatation has not been established in humans.[8] The significant augmentation of angiotensin II-induced vasoconstriction after m-cholinoceptor blockade in controls observed in this study is consistent with a substantial influence of cholinergic baroreflex vasodilatation on vascular tone. Because muscle sympathetic adrenergic nerve activity is already greatly reduced by small increases in mean aortic pressure,[21] this may indicate an important role of an additional cholinergic baroreflex vasodilatation during moderate and severe pressure increases. M-cholinoceptor blockade alone failed to produce an increase in blood pressure and resistance in controls in this study as well as in others.[10,22,23] This may indicate the absence of a major tonic cholinergic modulation of vascular tone at rest (Figure 3).

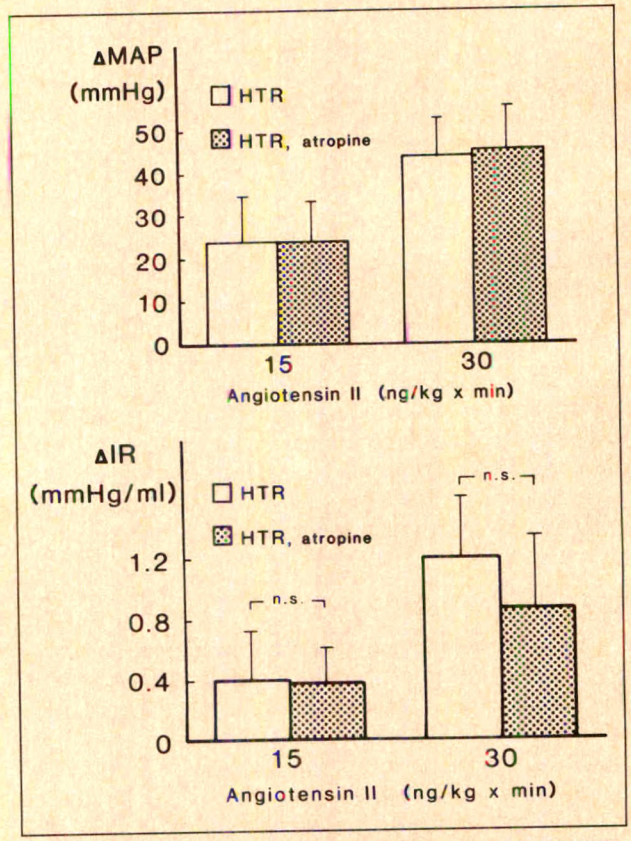


FIGURE 2. Increases in mean arterial blood pressure (ΔMAP), instantaneous resistance (ΔIR) in heart transplant recipients (HTR, n = 11) and in atropine-pretreated heart transplant recipients (HTR, atropine, n = 11) during infusion of 15 and 30 ng/kg · min of angiotensin II. After m-cholinoceptor blockade no additional increase in blood pressure and resistance is seen. n.s. = not significant.

Myocardial contractility did not differ in transplanted and innervated hearts with and without m-cholinoceptor blockade, thus excluding an influence of differences in myocardial contractility on the differences in angiotensin II-induced blood pressure increases. This has been observed previously.[17] An atropine-induced increase in heart rate does not induce an increase in blood pressure or resistance at rest.[10,22] In addition, a pacemaker-induced duplication of heart rate does not change blood pressure response to vasoconstriction.[10] Therefore, an influence of heart rate variations on results obtained in the present study can be excluded.

Cholinergic baroreflex vasodilatation after heart transplantation: LOCALIZATION OF THE BARORECEPTOR: The supersensitivity to angiotensin II-induced vasoconstriction in heart transplant recipients was not further augmented after m-cholinoceptor blockade, but was induced by this specific condition in controls. Hence, supersensitivity is most probably caused by the absence of a cholinergic vasodilatation capacity after heart transplantation due to afferent denervation of the ventricular baroreceptor. The ventricular baroreceptor is certainly involved in mediating reflex vasodilatation.[6–8,12] However, mediation of a cholinergic component of vasodilatation, until now, was unknown. In contrast to baroreceptor-mediated vasoconstriction,[7,8] mutual baroreceptor compensation in reflex vasodilatation, at most, is only incomplete.[8,21] The present study is likely to demonstrate that the cholinergic part of reflex vasodilatation is exclusively mediated by the ventricular baroreceptor and, therefore, reveals no baroreceptor redundancy.

Unspecific confounding influences: The conclusions of the present study have to take into consideration the function of the arterial baroreceptors, the nonspecific and acetylcholine-mediated vasodilatation capacity, and a possible interference between cyclosporine A and angiotensin II-induced vasoconstriction.

A normal function of the arterial baroreceptors after heart transplantation in response to both unloading and loading procedures has been documented in several studies.[2,4,5,24] Preservation of a normal nonspecific vasodilatation after heart transplantation has been observed.[24] Acetylcholine-induced, endothelium-dependent vasodilatation may be impaired in arterial hypertension,[25] and additionally by cyclosporine A.[26] However, this does not explain the complete inhibition of cholinergic vasodilatation. Moreover, acetylcholine released from the cholinergic nerves most probably does not reach the endothelium.[27] This indicates that cholinergic reflex vasodilatation may act independently of the endothelium.[13,27]

Cyclosporine A reveals a vasoconstricting effect due to an increase in sympathetic activity[2,26,28] and modulation of the intracellular calcium homeostasis.[26,28] However, several studies in experimental animals indicate

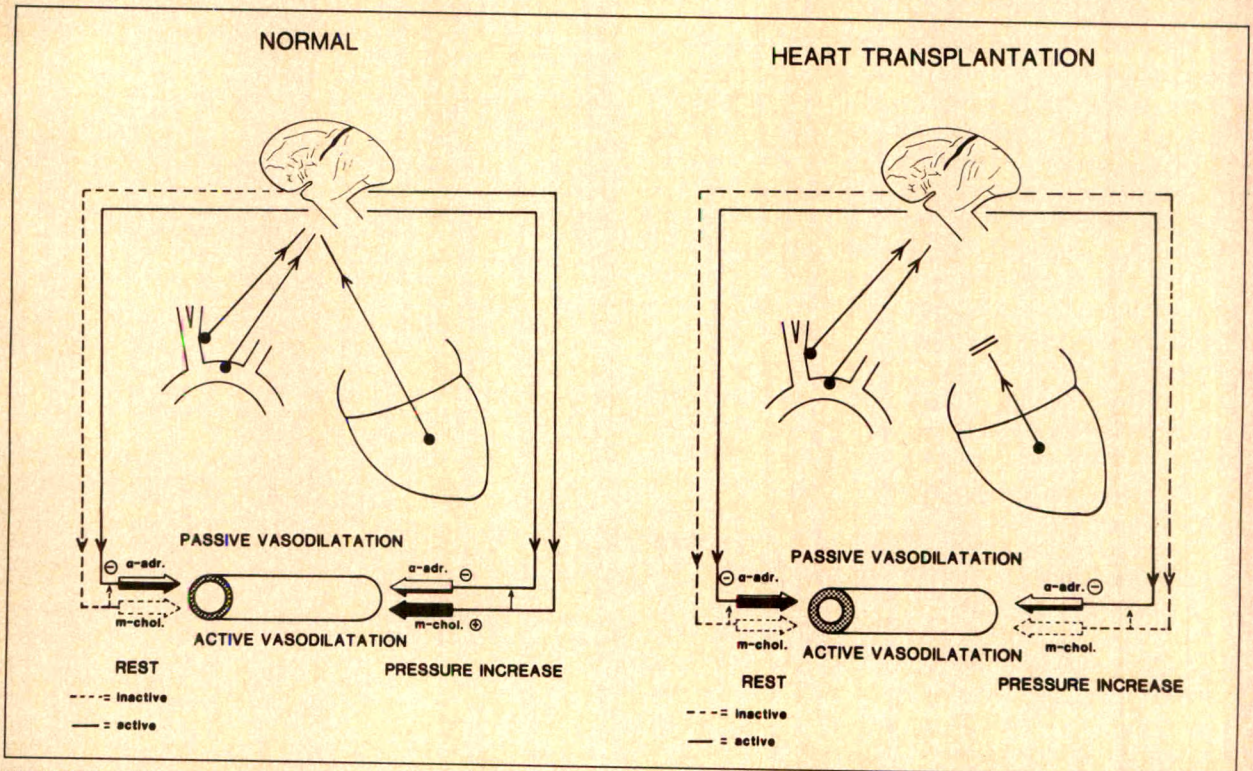


FIGURE 3. Schematic showing baroreflex control of vasodilatation at rest *(left)* and during pressure increase *(right)* in healthy humans (normal) and heart transplant recipients (heart transplantation). In healthy humans at rest, tonic restraint of the arterial and ventricular baroreceptors on α-adrenergic vasoconstriction is present (α-adr., passive vasodilatation). M-cholinergic vasodilatation (m-chol., active vasodilatation) seems to be inactive at rest. During pressure increase, restraint on sympathetic adrenergic outflow is augmented. In addition, m-cholinergic vasodilatation is activated. In heart transplant recipients at rest, tonic restraint of the arterial, but not the ventricular, baroreceptors on α-adrenergic vasoconstriction is present. This may result in an increased vascular tone at rest. During pressure increase, restraint on α-adrenergic vasoconstriction may be augmented. However, m-cholinergic vasodilatation remains inactive, since it originates exclusively from the ventricular baroreceptor, which is denervated.

that cyclosporine A in vivo does not induce an increased vasoconstriction in response to norepinephrine, angiotensin II or arginine-vasopressin.[28,29] In addition, the effects of cyclosporine-A on vasoconstrictor sensitivity would not explain the absence of an augmentation of the pressure response after m-cholinoceptor blockade in heart transplant recipients. On the other hand, the pressure increase induced by angiotensin II is the same in heart transplant recipients and controls after m-cholinoceptor blockade, suggesting that interruption of the cholinergic vasodilatation alone completely explains the vasoconstrictor supersensitivity in heart transplant recipients. Therefore, it is not unreasonable to assume that cyclosporine A does not increase vascular sensitivity to angiotensin II and does not interact with the specific reflex-mediated cholinergic vasodilatation during angiotensin II-induced pressure increase.

Thus, the vasoconstrictor supersensitivity after heart transplantation found in this study is caused by the absence of a specific atropine-sensitive mechanism (i.e., cholinergic vasodilatation) due to denervation of the ventricular baroreceptor. This occurs (1) in the presence of a significantly increased blood pressure and resistance response to angiotensin II after m-cholinoceptor blockade in controls and a complete lack thereof in heart transplant recipients; (2) in the presence of innervated, intact arterial baroreceptors; and (3) in the absence of an interaction between cyclosporine A and angiotensin II (Figure 3).

Regulation of blood pressure at rest after heart transplantation: Several studies indicate an aggravation of the cyclosporine A-induced increase in sympathetic adrenergic outflow, systemic vascular resistance and arterial hypertension in heart transplant recipients at rest.[2,3] From studies in experimental animals there is ample evidence of a tonic-restraining influence on sympathetic adrenergic outflow to the circulation, mediated by both cardiac and arterial baroreceptors.[6–8] Experimental ventricular baroreceptor blockade results in an increase in sympathetic adrenergic outflow and blood pressure.[7]

These observations strongly support the hypothesis that baroreflex modulation of the vascular tone is altered also at rest after cardiac denervation. This is most probably due to a loss of the part of tonic restraint on sympathetic adrenergic outflow, which originates from the ventricular baroreceptor. Therefore, it is not unreasonable to conclude that in addition to the complete loss of cholinergic vasodilatation during pressure increase, impairment of the restraint on sympathetic adrenergic outflow to the vascular bed is present in heart transplant recipients, resulting in an increased vascular tone at rest (Figure 3). This offers the missing explanation for aggravation of cyclosporine A-induced hypertension in heart transplant recipients.

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Evaluation of Changes in Standard Electrocardiographic QRS Waveforms Recorded from Activity-Compatible Proximal Limb Lead Positions

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Proximal limb lead positions are currently used for activity-compatible electrocardiographic monitoring of myocardial ischemia. Two previously described systems for alternate limb lead placement were studied in patients with and without QRS evidence of healed anterior or inferior myocardial infarction. An innovative method was used to simultaneously record 6 standard and 6 modified limb leads, and 3 standard and 3 modified precordial leads on a standard digital electrocardiograph. Both alternate lead placement systems showed rightward frontal plane axis shift and diminished Q-wave durations in lead aVF compared with those of their simultaneous standard controls. Furthermore, potential differences between the standard distal limb lead sites and 5 more proximal sites were explored along each limb. Differences along the left arm were accentuated relative to those along the right arm owing to differences in proximity of the arms to the myocardium. Along the lower limb, an anterior site showed less deviation from standard than did a more lateral site. It is imperative that recordings from alternate sites be labeled accordingly so that their output cannot be confused with that obtained from standard sites.

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The 12-lead electrocardiogram with its standard electrode placement distally on the limbs forms the basis for both manual and automated electrocardiographic analysis. Serial comparison of electrocardiograms also requires this standard lead placement. Alternate lead placements have been developed for activity-compatible monitoring of myocardial ischemia. The Mason-Likar[1] and Lund[2] lead placements use sites that provide stable recordings during exercise. The Mason-Likar positions yield electrocardiograms with QRS complexes that differ so much from the standard that they are invalid for many diagnostic purposes.[2,3] Recently, Krucoff et al[4] adopted an intermediate position for the limb leads for 12-lead ischemia monitoring with the EL-I electrocardiograph developed by Mortara Instrument (Milwaukee, Wisconsin). Recordings from alternate sites often are not accompanied by alternate labeling of leads.[5] The purposes of this study were: (1) to compare the deviation from standard QRS waveforms resulting from the Lund[2] and Krucoff[4] lead placements, and (2) to explore alternate limb lead sites to identify the most proximal positions that provide minimal potential differences compared with those of the standard distal site.

METHODS

Electrocardiographic recordings: A standard digital 12-lead electrocardiograph (Sicard 740, Siemens-Elema AB, Solna, Sweden) was used to obtain 2 simultaneous electrocardiograms for the purpose of comparing standard versus activity-compatible recordings (Figure 1). An innovation was required to simultaneously obtain 6 standard and 6 modified limb leads, and 3 standard and 3 modified precordial leads. This method required sacrificing 3 of the standard precordial leads (V_1, V_4 and V_6) so that those 3 electrodes could be placed at the proximal limb positions used in the activity-compatible system. This process was performed for both the Lund and Krucoff modified recording methods (Table I). The mathematical basis for the signals of the modified lead positions is contained in the appendix.

Alternate limb lead sites were explored at 5 positions along each extremity by recording the potential differences versus the standard distal sites (Table I). Alternate sites 1 and 2 on the arms are located between Krucoff and Lund positions, but on the left leg are located distal to the other 3 sites.

Study patients: Patients were selected from those admitted to the cardiology ward of the Lund University Hospital during a 6-month period in 1989 and 1990. Groups of 10 patients each were identified using the manual screening criteria of Anderson et al[6] for anterior (V_2: any Q or R ≤0.1 mv and ≤10 ms) and inferior (aVF: Q ≥30 ms) myocardial infarctions (MIs). The 3 groups were: no MI (neither criterion); anterior MI (anterior criterion only); inferior MI (inferior criterion only).

TABLE I Limb Lead Sites

	Arm	Leg
Mason-Likar	2 cm below clavicle in MCL	Midway between costal margin and anterior iliac crest in the AAL
Krucoff	Lateral extent of clavicle	On iliac crest in the MAL
Lund	Lateral on arm at level of axillary fold	On iliac crest in the AAL
Alternate 1	Acromion process of scapula	Midway between iliac crest and greater femoral trochanter in MAL
Alternate 2	Midway between acromion and Lund position on lateral arm	Greater femoral trochanter

AAL = anterior axillary line; MAL = midaxillary line; MCL = midclavicular line.

TABLE II Q-Wave Duration in aVF (ms) for Patients with Inferior Infarct

Pt. No.	Standard 1	Lund	Standard 2	Krucoff
1	59	44	51	34
2	33	26	30	—
3	34	31	33	32
4	79	26	78	21
5	58	21	40	32
6	—	—	—	37
7	45	34	43	38
8	50	46	50	46
9	51	46	53	42
10	29	30	32	30

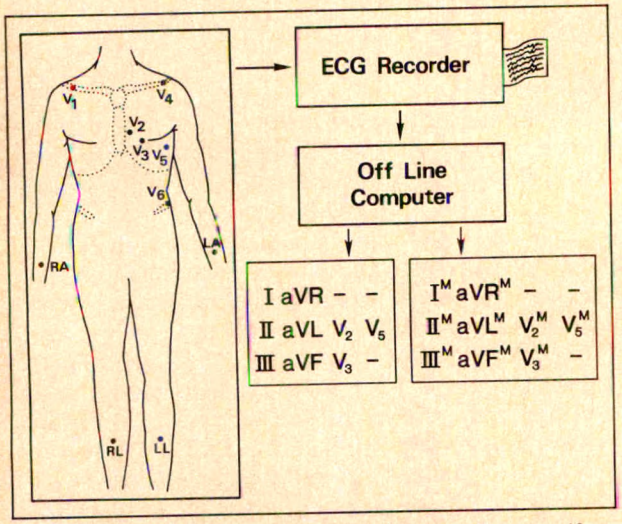


FIGURE 1. Two simultaneous 9-lead electrocardiograms (1 with standard limb lead and the other with alternate sites) were obtained by computer processing of 12-lead electrocardiogram with indicated electrode placements. The V_1, V_4 and V_6 electrodes have been moved to alternate limb lead positions. ECG = electrocardiographic; M = modified: signals obtained using these sites as limb lead positions.

Data analysis: Two sets of 2 simultaneously recorded 9-lead electrocardiograms per patient were obtained, as described previously. Quantitative differences in Q-wave durations in lead aVF were determined by comparing both the Lund and Krucoff recordings with their respective controls (standards 1 and 2). The quantitative extent of MI was estimated for each 9-lead recording using the complete Selvester QRS scoring system.[7] QRS scores were determined from leads V_2, V_3, V_5, I, II, aVL and aVF on each of the 4 recordings from the 3 different lead placement sites using the computer-measured waveform durations and amplitudes. QRS measurements were obtained with custom software, according to the recommendations of "Common Standards for Electrocardiography."[8] The frontal plane QRS axis was determined using QRS amplitudes in leads I, II and III, as described by Macfarlane and Lawrie.[9]

Variation in limb electrode site may also effect the appearance of a precordial lead recording, because the central terminal (average of potentials from the right and left arm, and left leg electrode sites) is used as the negative pole for leads V_1 to V_6. Such changes were documented by Sevilla et al.[3] The differences between the standard and each of the modified central terminals (see appendix) were determined. These differences were then used to quantify the influence of using these alternate lead systems on precordial lead waveforms.

RESULTS

Comparisons of Q-wave durations in lead aVF between standard and each of the 2 activity-compatible systems for the 10 patients with inferior MI are listed in Table II. A small R wave was detected by the computer before any negative deflection in 1 patient (no. 6). Q-wave durations in the 2 standard recordings differed by a mean of 4 ms in the 9 patients in whom a Q wave was identified. Diminished Q-wave durations were measured by both alternate systems in 8 (Lund) and 9 (Krucoff) recordings with mean decreases of 15 (Lund) and 13 (Krucoff) ms in duration.

Table III lists the QRS scores in the 3 groups comparing the 2 standard recordings and each standard with its simultaneous activity-compatible recording. Mean scores for the 2 standard recordings varied by 0.6, 0.8 and 0.8 points for the no, anterior and inferior MI groups, respectively. Variations between standard and both alternate systems were less than those in both the no MI and anterior MI groups. However, the mean difference within the inferior MI group between standard 1 and Lund was 1.4 points and between standard 2 and Krucoff was 1.7 points. The differences were usually caused by loss of QRS points with the alternate systems.

Distributions of differences between frontal plane QRS-axis measurements are shown in Figure 2. Twen-

TABLE III Total QRS Points

Pt. No.	Standard 1	Lund	Standard 2	Krucoff
No MI				
1	0	0	0	2
2	1	1	1	1
3	0	0	0	0
4	1	0	0	0
5	0	0	0	0
6	3	0	0	0
7	0	0	2	0
8	0	0	0	0
9	0	0	0	0
10	0	0	0	0
Anterior MI				
1	2	3	2	2
2	3	3	5	3
3	5	5	5	6
4	4	4	4	4
5	4	4	3	4
6	2	2	3	3
7	3	3	2	2
8	4	4	4	4
9	9	10	7	9
10	3	2	2	2
Inferior MI				
1	3	2	3	1
2	1	0	2	0
3	2	1	2	2
4	6	3	4	2
5	7	5	7	6
6	1	1	1	4
7	6	4	6	4
8	6	5	5	5
9	6	5	7	5
10	1	2	4	1

MI = myocardial infarction.

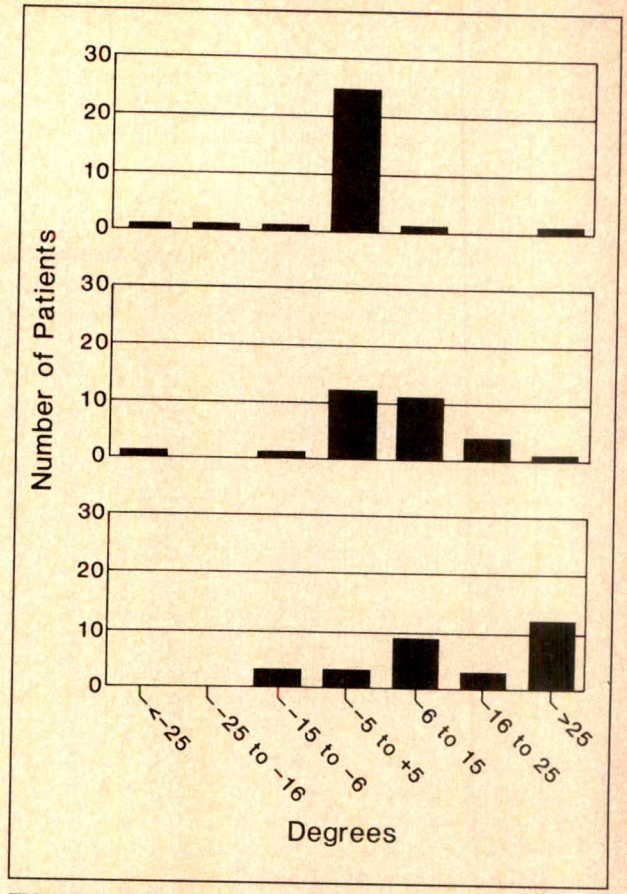


FIGURE 2. Differences between frontal plane axis measurements. *Top*, standard 1 versus 2; *middle*, standard 1 versus Lund; and *bottom*, standard 2 versus Krucoff.

ty-five of the 30 patients (83%) showed ≤5° differences between axis determinations in the 2 standard recordings. There was similar agreement for 12 patients (40%) with standard 1 versus Lund, and for 3 patients (10%) with standard 2 versus Krucoff. Both alternate systems showed a tendency toward rightward axis shift. However, this difference was >25° in only 1 patient (3%) with the Lund system versus in 12 (40%) with the Krucoff system.

Figure 3 presents the differences between the voltages of the central terminals generated by Lund versus standard 1 and by Krucoff versus standard 2 lead placement systems. Greater differences are apparent for the Krucoff method, with a median of 108 versus 28 μV for the Lund method.

Figure 4 presents peak-to-peak voltage differences between the standard and various proximal recording sites on the right and left arms. The proximal positions on the left arm produce roughly 3 times as much variation in peak-to-peak voltage differences as those on the right. Use of the Krucoff site on the right side would achieve a median voltage difference of 100 μV whereas more distal placement at a site midway between the acromion and the Lund position would be required to achieve this level on the left arm. A similar format is used in Figure 5 to present voltage differences from the 5 sites on the left leg. Recording from distal to both Lund and Krucoff sites would be needed to achieve the threshold of a median difference of 100 μV.

DISCUSSION

Sevilla et al[3] documented the limitations of recording from Mason-Likar sites regarding diagnosis of MI, with only one third of patients with inferior MI apparent by standard recordings retaining diagnostic QRS changes. In the present study, although both of the alternate systems produced diminished Q-wave durations in lead aVF, these fell short of a 30 ms diagnostic threshold[7] in only 1 of 9 instances with Krucoff and in 3 of 9 with Lund sites.

Falsely low estimates of inferior MI size were demonstrated using Mason-Likar recordings,[3] and similar results are apparent in the present study. Approximately one third of all points attained with the Selvester QRS scoring system for the inferior location were lost using each of the alternate systems.

Remarkably similar QRS scores were achieved in both the normal and anterior MI groups when standard and alternate systems were compared. Sevilla et al[3] revealed falsely positive diagnosis of both lateral and apical infarctions by Mason-Likar recording. In the present study, only 1 patient achieved additional QRS

points (lateral) with an alternate recording system (Table III).

Sevilla et al[3] demonstrated a marked rightward axis shift in the frontal plane with a mean change of approximately 50°. A similar result was apparent using the Krucoff site, with 40% of patients having a rightward shift of ≥25°. The axis remained much more stable using Lund sites, with most of the rightward shifts being <15° from standard. The probable cause of this lesser deviation of frontal plane axis is the smaller potential differences observed between standard and Lund versus standard and Krucoff sites (Figures 4 and 5).

The horizontal plane changes (as expressed by the differences in central terminals) are small relative to those in the frontal plane. However, it is possible that use of activity-compatible recording sites could alter the amplitude of a waveform sufficiently to effect its attainment of a criterion threshold. The reason for the greater differences in central terminal voltages resulting from Krucoff versus Lund sites also becomes apparent from observing the data presented in Figures 4 and 5. For each of the 5 lead positions, differences on the left arm are magnified over those on the right arm because of the proximity of that limb to the myocardium.

The more anterior position on the iliac crest (Table I) of the Lund site for the left leg electrode results in less potential difference than that resulting from the Krucoff site. Since movement to the more distal greater trochanteric site is needed to achieve a voltage difference <100 μV, it would be important for a future study to determine if such placement would result in retaining Q-wave durations in lead aVF.

Of the 3 major sites of MIs, only the inferior is represented primarily in frontal plane leads. None of the current activity-compatible lead systems are capable of retaining the important diagnostic Q-wave durations in lead aVF. Therefore, when an electrocardiographic recording at rest is desired before performance of an exercise test, the standard rather than the activity-compatible limb lead sites should be used. To facilitate use of these alternate sites for continuous 12-lead monitoring, further studies are needed to develop a method for transformation from the alternate to the standard waveforms either for each individual or preferably by a global transformation that would be applicable to all. It is not recommended that separate diagnostic criteria be developed for each alternate lead system.

This study indicates that it is imperative that recordings from alternate sites be labeled accordingly so that their output cannot be confused with that obtained from standard sites. Since the present study investigates only QRS waveforms, a further study is needed to determine if similar variations occur in ST segments and T waves, using patients with acute rather than chronic ischemic heart disease.

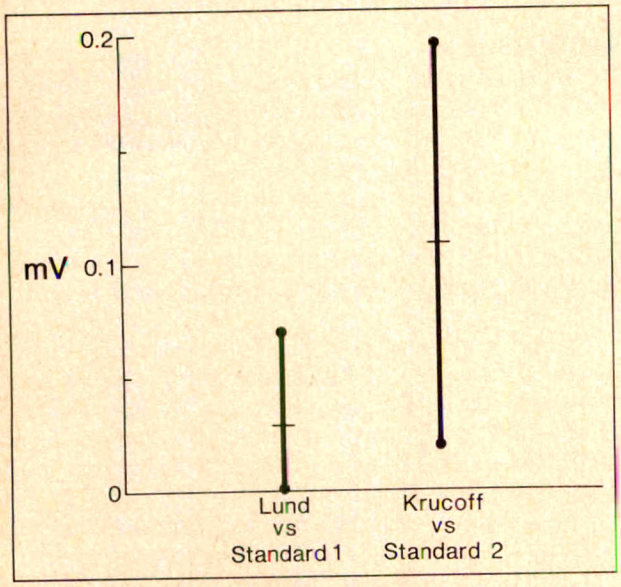


FIGURE 3. Peak-to-peak voltage differences between central terminals resulting from recording from alternate limb lead sites. *Horizontal lines* indicate medians, and *vertical lines* indicate ranges.

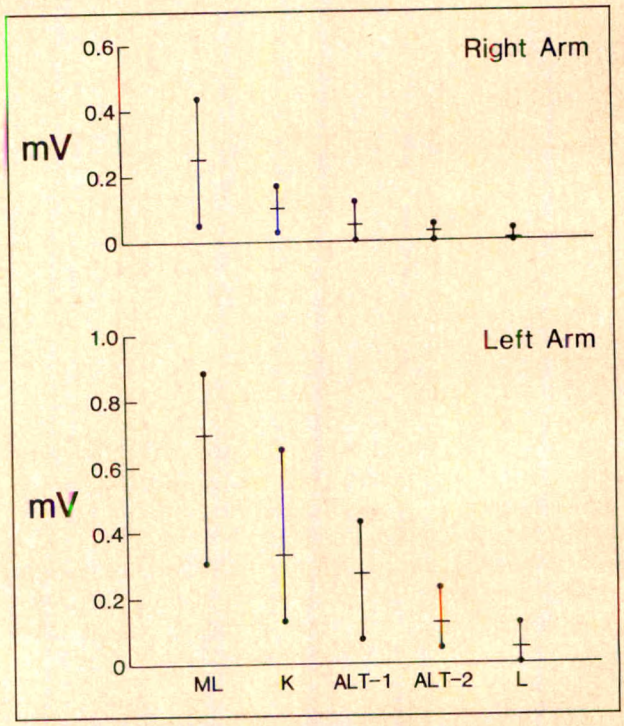


FIGURE 4. Peak-to-peak potential differences between standard distal lead placement sites and 5 alternate more proximal sites are presented for right *(top)* and left *(bottom)* arms. Medians are indicated by *horizontal lines*, and ranges by *vertical lines*. ALT = alternate; K = Krucoff; L = Lund; ML = Mason-Likar.

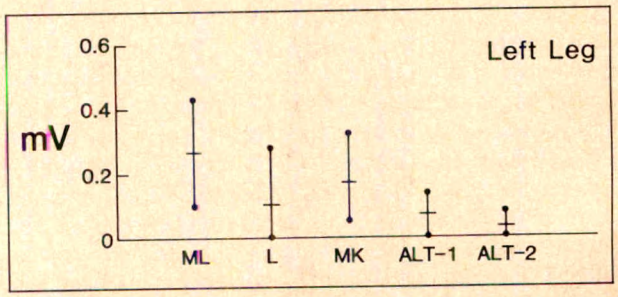


FIGURE 5. Format and abbreviations as in Figure 4.

APPENDIX

Let R^M, L^M and F^M denote potentials at the right and left arm, and left leg positions, respectively, and I^M and II^M, the limb leads of a modified lead system. CT^S and CT^M are the central terminals of the standard and modified systems, respectively. C_2, C_3 and so forth denote potentials at precordial recording sites. Finally, the signals recorded from the modified right and left arm, and left leg positions (using the standard central terminal as reference) are denoted X_1, X_4 and X_6, respectively.

Then: $X_1 = R^M - CT^S$; $X_4 = L^M - CT^S$; $X_6 = F^M - CT^S$; and $V_2 = C_2 - CT^S$; $V_2{}^M = C_2 - CT^M$, and so forth.

By definition: $I^M = L^M - R^M = L^M - CT^S - (R^M - CT^S) = X_4 - X_1$; $II^M = X_6 - X_1$.

The remaining 4 modified limb leads are calculated from I^M and II^M.

For calculating the precordial leads of the modified system its central terminal is used. This is defined by: $CT^M = (R^M + L^M + F^M)/3$.

Using the above relations: $CT^M = (X_1 + CT^S + X_4 + CT^S + X_3 + CT^S)/3 = (X_1 + X_4 + X_6)/3 + CT^S$. This can be rewritten: $CT^M - CT^S = (X_1 + X_4 + X_6)/3$.

Finally: $V_2{}^M = C_2 - CT^M = (C_2 - CT^S) - (CT^M - CT^S) = V_2 - (X_1 + X_4 + X_6)/3$.

Thus, each of the V_2, V_3 and V_5 leads of the modified system is calculated by subtracting the average of the X_1, X_4 and X_6 signals from the corresponding V-lead signal.

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Rapidity and Duration of Platelet Suppression by Enteric-Coated Aspirin in Healthy Young Men

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The recent demonstration of aspirin's ability to prevent and reduce the severity of myocardial infarction has led to a marked increase in its use and to a need for information regarding the time-course of onset and offset of its antiplatelet effect. A study of healthy men was conducted to determine (1) the rapidity of onset of inhibition of platelet aggregation in response to adenosine diphosphate, and thromboxane A_2 production after chewed enteric-coated aspirin (325 mg, n = 10); and (2) the duration of platelet inhibition after cessation of enteric-coated aspirin (325 mg) every other day for 14 days (n = 10). When chewed, enteric-coated aspirin greatly inhibited platelet aggregation response to adenosine diphosphate and thromboxane A_2 production within 15 minutes. Complete recovery of platelet aggregation occurred in half of the subjects by day 3, and in 80% of the subjects by day 4; the platelet response was not affected by exercise. This study demonstrates a rapid onset of aspirin's antiplatelet effect and provides information relevant for optimal timing of initiation of aspirin for acute conditions such as myocardial infarction and unstable angina, and cessation of aspirin before surgery.

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Although regular and enteric-coated aspirin produce equivalent antiplatelet effects,[1,2] the time to onset of antiplatelet effect is less after ingestion of regular aspirin (30 minutes)[3] than after enteric-coated aspirin (2 to 3 hours).[1] A longer time to antiplatelet effect may be undesirable in acute myocardial infarction or unstable angina when rapid onset is needed. This could limit the value of enteric-coated aspirin, which otherwise is a desirable therapy because it has fewer gastrointestinal side effects than regular aspirin.[4,5] The delay in onset of activity may be eliminated by chewing the first tablet of enteric-coated aspirin; however, the rapidity of onset of activity with this method of administration has not been previously studied.

The time to offset of aspirin's antiplatelet effect after cessation of aspirin is also clinically relevant for the increasing number of patients scheduled to undergo elective surgery who are receiving long term therapy with aspirin. The dilemma of when and if to discontinue aspirin is particularly evident for patients who undergo coronary artery bypass grafting, since the use of aspirin in the immediate preoperative period is associated with increased intraoperative blood loss[6,7]; yet these patients may benefit from the cardioprotective effect of aspirin.

The present study determines (1) the time to onset of inhibition of platelet aggregation and serum thromboxane A_2 production after chewed enteric-coated aspirin (325 mg), and (2) the duration of action of platelet inhibition after cessation of oral enteric-coated aspirin (325 mg) given every other day.

METHODS

The study was conducted in 18 healthy, male volunteers (aged 20 to 33 years) who were nonsmokers, had taken no aspirin or other medication during the 2 weeks before the study and had given informed consent. This initial study was confined to men to eliminate the possibility of cyclic variations in platelet aggregation related to the menstrual cycle. The study was approved by the Institutional Review Board of the Brigham and Women's Hospital, and was conducted in the Ambulatory Clinical Research Center of the Brigham and Women's Hospital.

Phase I: time to onset of platelet inhibition: To determine the rapidity of onset of inhibition of platelet aggregation and thromboxane A_2 production, 10 subjects were studied before, and 15, 30 and 60 minutes after they chewed 325 mg of enteric-coated aspirin (Ecotrin, SmithKline Beecham).

Phase II: time to offset of platelet inhibition: To determine the time course of recovery of platelet aggrega-

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bility after cessation of enteric-coated aspirin, at rest and after bicycle exercise, 10 subjects (2 of whom participated in the time to onset of study) received 325 mg of enteric-coated aspirin before breakfast every other day for 14 days. Blood samples were obtained immediately before and after enteric-coated aspirin was initiated, and at 2, 3 and 4 days after the last dose. On each study day, blood samples were obtained immediately before and after bicycle exercise. The exercise was performed in a seated position on a cycle ergometer. An initial work load of 50 W was increased by 50 W after each 3 minutes of exercise. Subjects exercised to approximately 90% of maximal working capacity (mean exercise time 10.3 ± 0.8 minutes).

BLOOD SAMPLE COLLECTION: Blood samples were obtained without stasis from an antecubital vein with use of a 19-gauge butterfly needle. Separate venipunctures were performed at each time point. For platelet aggregation studies and platelet counts, a 27 ml sample of whole blood was collected in a plastic syringe containing 3 ml of 3.8% sodium citrate (9:1 vol:vol). A 3 ml sample was collected for catecholamine analysis, a 5 ml blood sample was collected for tissue plasminogen activator antigen measurement in a syringe containing 3.8% sodium citrate, and a 5 ml sample was collected for serum thromboxane B_2 and 6-keto-prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$) determinations.

PLATELET AGGREGATION STUDIES: Blood samples were centrifuged at 160 × g for 10 minutes to obtain platelet-rich plasma. The platelet-rich plasma was removed by pipette and transferred to a polystyrene tube that was tightly capped. Platelet-poor plasma was obtained by centrifuging whole blood in a microcentrifuge at 14,000 × g for 8 minutes. Aggregometry was performed according to the method of Born,[8] using a Biodata Pap-4 aggregometer (Hatboro, Pennsylvania) at 37°C with 1 ml siliconized cuvettes and rotating bars (1,200 rpm). The aggregometer was adjusted before each experiment so that platelet-rich plasma gave no light transmission and platelet-poor plasma gave 100% light transmission. Adenosine diphosphate (Sigma) and epinephrine (Sigma) were used as aggregating agents; the final concentrations of adenosine diphosphate and epinephrine ranged from 0.005 to 30 μM. To minimize inherent variations in aggregation response, the studies using adenosine diphosphate and epinephrine were initiated 45 and 60 minutes after venipuncture and were completed within 90 minutes of the venipuncture. For each subject, a range of fixed concentrations of agonist was studied in a stepwise fashion. Aggregation tracings were analyzed to determine the threshold concentration, defined as lowest concentration of each agonist, sufficient to produce biphasic aggregation.

Inhibition of platelet aggregation was defined as (1) complete, if biphasic aggregation was not produced by either 30 μM of adenosine diphosphate or epinephrine; (2) partial, if biphasic response was produced by >5.0 and <30 μM of either of the 2 agents; and (3) absent, when biphasic response was produced by <5.0 μM of either agonist. The platelet count in platelet-rich plasma was determined with a model ZF Coulter Counter (Coulter Electronics, Hialeah, Florida).

Thromboxane A_2 and prostacyclin production were determined by radioimmunoassay of serum thromboxane B_2 and 6-keto-$PGF_{1\alpha}$, their stable metabolites (James McDonald, AIA Reagents, Denver, Colorado). These assays were performed on venous blood collected without anticoagulant and incubated at 37°C for 1 hour. Serum was stored at −20°C until assayed. Aspirin produced inhibition of serum thromboxane B_2 production similar to that reported for plasma.[2]

Plasma epinephrine and norepinephrine levels were measured using a single-isotope radioenzymatic method based on a modification of the method of Peuler and Johnson.[9] Tissue plasminogen antigen was measured using an enzyme-linked immunoassay technique (Stago, Ansieres, France).

Statistical analysis: Comparisons between mean values were made with the Wilcoxon signed rank test for paired values. All deviations from mean are expressed as standard errors. A 2-tailed p value <0.05 was regarded as statistically significant.

RESULTS

Phase I: time to onset of platelet inhibition: PLATELET AGGREGATION (FIGURES 1 AND 2): Before enteric-coated aspirin was administered the maximum threshold concentration for biphasic platelet aggregation in any subject was 5 μM for adenosine diphosphate and 3 μM for epinephrine (mean threshold concentration, adenosine diphosphate 2.8 ± 0.4 μM and epinephrine 1.5 ± 0.4 μM). Fifteen minutes after chewing 325 mg of enteric-coated aspirin, inhibition of biphasic platelet aggregation induced by both adenosine diphosphate and epinephrine was complete in 7 subjects, partial in 2 subjects, and absent in 1. By 30 minutes, inhibition of the biphasic platelet response to both agonists was complete in all subjects. Inhibition persisted at 60 minutes.

SERUM THROMBOXANE B_2 PRODUCTION (FIGURE 3): Chewed enteric-coated aspirin markedly decreased serum thromboxane B_2 production within 15 minutes,

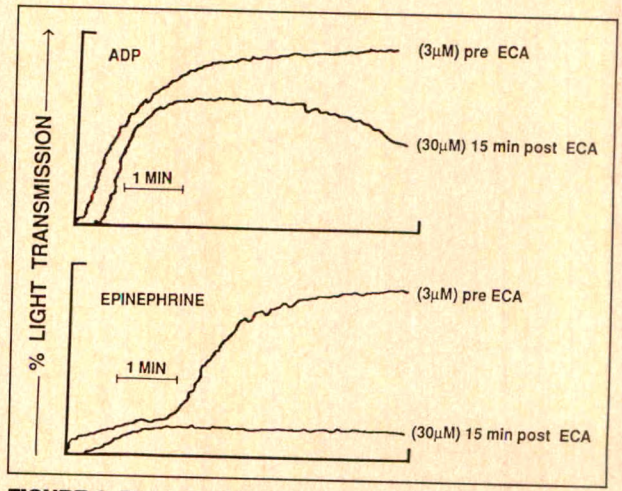


FIGURE 1. Platelet aggregatory response to adenosine diphosphate (ADP) and epinephrine in 1 subject before and 15 minutes after enteric-coated aspirin (ECA). Increasing aggregation is shown by an increase in light transmission. Platelets obtained 15 minutes after the subject chewed 325 mg of enteric-coated aspirin did not aggregate in response to adenosine diphosphate or epinephrine in concentrations of 30 μM.

from 244 ± 43.6 before to 11.9 ± 1.4 ng/ml after therapy ($p < 0.01$). Production remained suppressed at 30 and 60 minutes after therapy (9.8 ± 4.5, and 2.5 ± 1.4 ng/ml, respectively).

SERUM 6-KETO-$PGF_{1\alpha}$: Chewed enteric-coated aspirin significantly decreased serum 6-keto-$PGF_{1\alpha}$ production within 15 minutes, from 1,133 ± 221 before to 129 ± 18 pg/ml after therapy ($p < 0.01$). Production remained suppressed at 30 and 60 minutes after therapy (100 ± 19 and 67 ± 12 pg/ml, respectively).

TISSUE PLASMINOGEN ACTIVATOR ANTIGEN AND PLASMA CATECHOLAMINES: Neither tissue plasminogen antigen nor plasma catecholamine levels were significantly altered by enteric-coated aspirin. Tissue plasminogen activator levels were 4.6 ± 0.8 before and 5.8 ± 1.4 ng/ml 15 minutes after therapy. Plasma epinephrine levels were 44 ± 6 before and 39 ± 5 pg/ml 15 minutes after therapy, whereas plasma norepinephrine levels were 303 ± 36 before and 274 ± 32 pg/ml 15 minutes after therapy with enteric-coated aspirin.

Phase II: time to offset of platelet inhibition (Figure 4): Aggregability remained at least partially suppressed in all subjects at day 2 (48 hours after the last dose of enteric-coated aspirin). By day 3 complete recovery of platelet aggregation was present in 4 of 10 subjects in response to adenosine diphosphate, and in 5 of 10 subjects in response to epinephrine. By day 4, complete recovery of platelet aggregation response had occurred in 8 of 10 subjects in response to adenosine diphosphate, and in 7 of 10 subjects in response to epinephrine.

Effect of exercise: There was a statistically significant increase in platelet count in platelet-rich plasma after bicycle exercise. Before enteric-coated aspirin therapy the mean platelet count increased with exercise from 193,000 ± 45,000 to 291,900 ± 21,000/ml ($p < 0.05$). Two days after therapy with enteric-coated as-

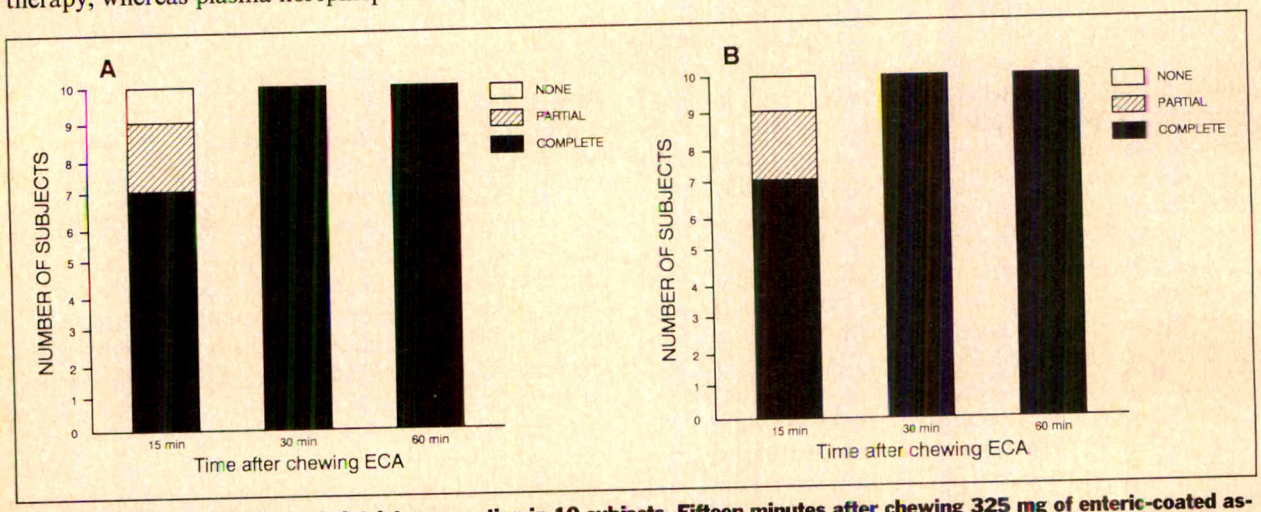


FIGURE 2. Time to inhibition of platelet aggregation in 10 subjects. Fifteen minutes after chewing 325 mg of enteric-coated aspirin (ECA), inhibition of platelet aggregation induced by adenosine diphosphate *(panel A)* and epinephrine *(panel B)* was complete in 7 subjects, partial in 2 and absent in 1. By 30 and 60 minutes, complete inhibition of adenosine diphosphate and epinephrine was present in all subjects.

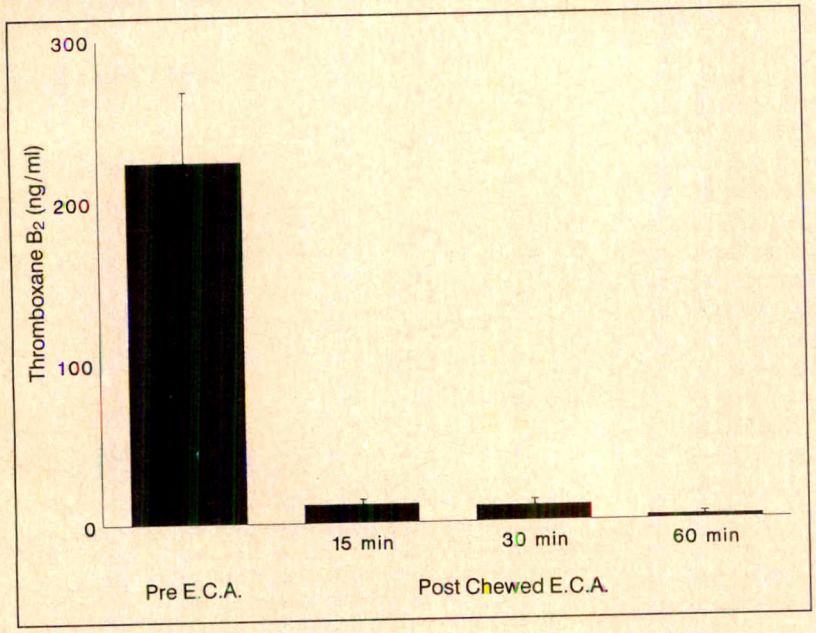


FIGURE 3. Serum thromboxane B_2 production. Chewed enteric-coated aspirin (E.C.A.) markedly suppressed thromboxane within 15 minutes.

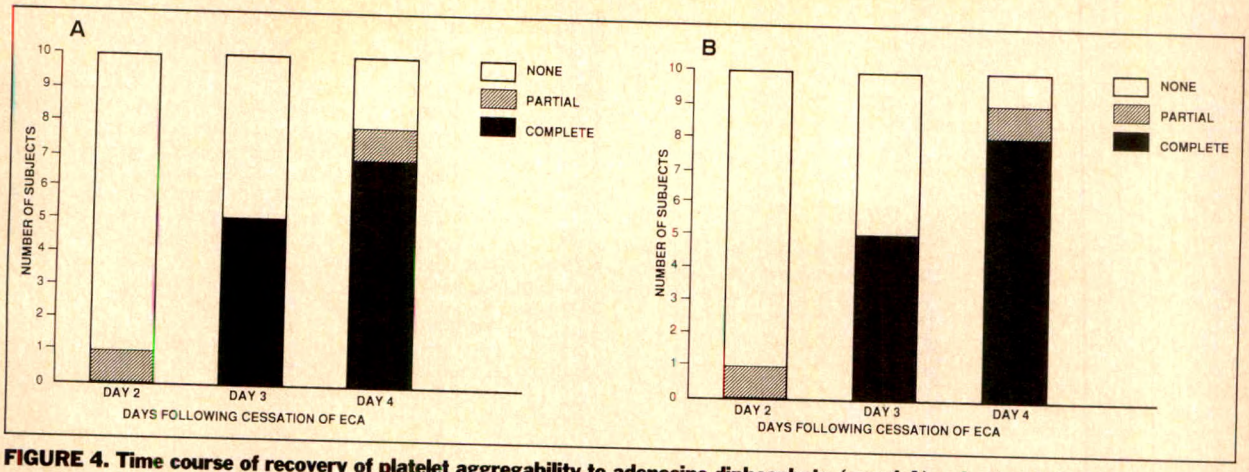


FIGURE 4. Time course of recovery of platelet aggregability to adenosine diphosphate *(panel A)* and epinephrine *(panel B)* after cessation of enteric-coated aspirin (ECA).

pirin was begun, the mean platelet count increased from 223,000 ± 11,400, to 322,300 ± 22,600/ml ($p < 0.05$) after exercise. Despite the increase in platelet count, exercise did not hasten recovery of platelet aggregation. Enteric-coated aspirin did not significantly alter platelet counts.

DISCUSSION

The present findings are, to our knowledge, the first to demonstrate that oral aspirin inhibits in vitro platelet aggregation in response to adenosine diphosphate within 15 minutes of ingestion. Paccioreti and Blak[3] previously noted onset of platelet inhibition in response to adenosine diphosphate, epinephrine and collagen 30 minutes after aspirin ingestion. Other investigators have reported platelet aggregation inhibition in response to collagen within 12 to 24 minutes after ingestion of aspirin; however, platelet aggregation response to adenosine diphosphate was not determined.[10,11] The response of platelets to adenosine diphosphate is of particular importance since data are now available linking in vitro adenosine diphosphate responsiveness of platelets to onset of myocardial infarction.[12–14]

The present study indicates that when chewed, an enteric-coated form of aspirin markedly inhibits platelet aggregation and thromboxane A_2 production within 15 minutes. This documents that the delay in onset of the effect of aspirin caused by enteric coating can be overcome by having the subject chew the preparation, essentially transforming the tablet into soluble form.

The widespread use of aspirin for prevention of cardiovascular disease[15–17] has led to the common clinical situation in which a patient taking aspirin must discontinue it before surgery. Because the cardioprotective benefits of aspirin are desired for as long as possible while persistence of the antithrombotic effects during surgery may cause excessive bleeding,[6,7] increased knowledge is needed of the duration of the impairment of platelet function caused by aspirin.

The antiplatelet effect of aspirin results from irreversible acetylation of cyclooxygenase and inhibition of thromboxane A_2 production. However, new platelets are released into the bloodstream at the rate of approximately 10% of total platelet number per day. At some point the new unacetylated platelets are present in sufficient quantity to restore normal platelet function. In the present study of healthy male subjects, complete recovery of platelet response to adenosine diphosphate and epinephrine occurred in approximately half of the subjects 72 hours after the last dose of aspirin and in 80% of subjects 96 hours after the last dose. Our results are consistent with those reported by Bradlow and Chetty.[18] It is possible that stress associated with surgery may hasten the return of normal platelet function, since adrenergic stimulation results in the release of younger more metabolically active platelets from the spleen.[19] In the present study, exercise with a resultant fourfold increase in plasma epinephrine did not overcome the inhibition of platelet aggregation by aspirin.

Thus, recovery of platelet function after aspirin therapy is relatively complete by 4 days and is not hastened by adrenergic stimulation. These data on duration of action can be combined with individual patient characteristics, including bleeding time, to determine the optimal time of aspirin cessation before surgery.

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Late, Out-of-Laboratory, Abrupt Closure After Angiographically Successful Directional Coronary Atherectomy

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The incidence of abrupt closure occurring out of the catheterization laboratory after angiographically successful percutaneous transluminal coronary angioplasty in native coronary arteries is approximately 2% (Table I).[1-5] Directional coronary atherectomy (DCA) has been associated with a lower incidence. This study reports our experience with abrupt closure after angiographically successful DCA.

From December 1989 to May 1991, DCA was performed electively at 302 coronary arterial sites in 284 patients. There were 10 protected left main, 175 left anterior descending, 46 left circumflex and 58 right coronary artery, and 15 saphenous vein grafts. The 15 vein grafts in 14 patients were excluded from analysis. A review of the clinical records, coronary angiograms, DCAs and in-hospital coronary events form the basis of this report.

All patients received 325 mg of aspirin before, the day of and after DCA. The heparinization routine was 10,000 to 15,000 units intravenously at the beginning of the procedure, with additional doses during the procedure to maintain an activated clotting time ≥300 seconds. Afterward, heparin was discontinued before the patient left the laboratory, and the femoral artery and venous sheaths were removed when the activated clotting time was <150 seconds. Patients did not leave the laboratory on a heparin drip. Heparin was not restarted after sheath removal. Intracoronary nitroglycerin and oral or sublingual calcium antagonists were administered to all patients. Coronary arteriography was performed in orthogonal views for quantitative analysis before and after DCA. DCA was performed with the Devices for Vascular Intervention, Inc. (Redwood City, California) device. For the right coronary artery, initially 11Fr, then 9.5Fr guiding catheters with side holes were used, and for the left coronary artery, 11Fr guiding catheters with side holes. Predilatation with a 2.0 mm balloon was performed in 113 patients (39%) before DCA to facilitate passage of the 6 or 7Fr atherectomy device, especially in de novo narrowings. Cuts were made at 10, 20 or 30 pounds per square inch, or a combination. The procedure was concluded and considered successful when the residual stenosis was <30%. Adjunct balloon angioplasty was performed in 62 patients (21%) when significant luminal irregularity or dissection was present. Lesions were graded according to the American College of Cardiology/American Heart Association task force criteria. Abrupt closure was defined as total occlusion of the treatment vessel within 48 hours of successful DCA.

Of the 270 patients, 228 (84%) were men and 42 (16%) were women. The mean age was 62 ± 10 years for men, and 65 ± 13 for women. In all, 81 patients (30%) had unstable angina, 14 (5%) had postinfarct angina, and 175 (65%) had stable angina. Thirteen patients received thrombolytic therapy (10 recombinant tissue plasminogen activator, 1 urokinase and 2 randomized in International Study of Infarct Survival-3) <6 weeks before the procedure.

There were 287 treatment sites in 270 patients. Of these sites, 177 (62%) were de novo narrowings, and 100 (38%) were restenotic narrowings. Of the 177 de novo narrowings, 11 (6%) were type A, 80 (45%) were type B and 86 (49%) were type C. A successful DCA was achieved in 252 sites (88%). The diameter stenosis before DCA was 73 ± 9%, and improved to 21 ± 9% after successful DCA (caliper measurements).

Of the 287 narrowings, 35 were unsuccessful or had an in-laboratory complication: inability to engage the guiding catheter (2 patients), inability to reach the lesion (5), inability to cross the lesion with the atherectomy device (16), inability to resect tissue (1), dissection (2), acute closure (3), distal spasm (1) and myocardial infarction (5). Twenty-eight of these patients had an alter-

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TABLE I Reported Incidence of Abrupt Closure Out of the Cardiac Catheterization Laboratory After Angiographically Successful Coronary Balloon Angioplasty

Series/Institution	Study Years	No. of Pts. (%)	Time to Closure in Hours (longest)
Sinclair et al[1]/Beth Israel Hospital	1981–1986	11 of 1,117 (0.98)	11 ± 2
Gabliani et al[2]/St. Louis University Hospital	1983–1987	22 of 1,238 (1.77)	27 ± 25 (96)
Ellis et al[3]/Emory University Hospital	1982–1986	99 of 4,342 (2.28)	(93)
Simpfendorfer et al[4]/Cleveland Clinic Foundation	1983–1985	32 of 1,500 (2.13)	5.2 ± 13 (72)
Hollman et al[5]/Emory University Hospital	1980–1982	20 of 935 (2.14)	8.6 ± 13.5 (56)
Total		184 of 9,132 (2.01)	

native revascularization procedure: balloon angioplasty (19 patients), placement of a coronary artery stent (2), or coronary artery bypass graft surgery (9), or a combination. There were 2 deaths; 1 from noncardiac causes and 1 after coronary artery bypass graft surgery.

There were 252 angiographically successful DCAs (88%). Late abrupt closure occurred in 6 patients (2.4%) after angiographically successful DCAs (Figure 1 and Table II). All occurred after the patient had left the catheterization laboratory. Mean time to closure was 19 ± 13 hours (4 at 12 hours, 1 at 16 hours, and 1 at 48 hours after the procedure). Three abrupt closures occurred in men, and 3 in women. Four of these patients had recent myocardial infarction (within 2 weeks) and postinfarction angina, and 2 had stable angina. Four patients had received thrombolytic therapy with tissue plasminogen activator (3 patients <16 days and one patient 42 days before DCA). All abrupt closures occurred in de novo narrowings (2 type A, 3 type B and 1 type C). All abrupt closures were predilated, and none had adjunct balloon angioplasty after DCA. No patient had a dissection after DCA. Abrupt closure was treated successfully by balloon angioplasty in 5 patients; 1 needed emergency bypass surgery. There were no deaths. In the 5 patients successfully reopened with balloon angioplasty, the total occlusion was crossed easily with conventional guide wires and balloon catheters. All acute occlusions had the angiographic appearance of intramural thrombosis without associated dissections.

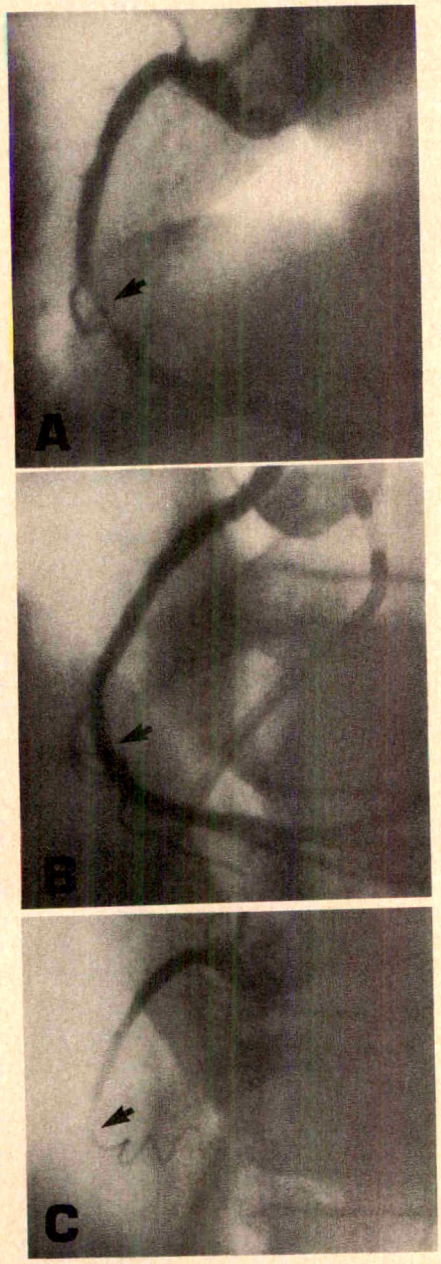


FIGURE 1. ***Panels A, B and C*** **from patient no. 3 with right coronary artery disease treated with directional coronary atherectomy (DCA). There is 75% narrowing before** ***(A, arrow)*** **and excellent angiographic result after** ***(B, arrow)*** **DCA. Twelve hours later, patient complained of chest pain with electrocardiographic changes showing acute inferior infarction. Coronary arteriography showed abrupt closure at DCA site** ***(C, arrow).***

Abrupt closure after successful DCA is thought to occur less often than after balloon angioplasty, possibly owing to a lower frequency of arterial dissections at the DCA site.[6] Causes for this are thought to be thrombus, dissection or nose cone injury.

As with balloon angioplasty, the incidence of abrupt closure after successful DCA may vary with operator experience. We report a large, single group experience with DCA. The incidence of abrupt closure was 2.4% in the 270 patients treated. Mean interval to closure was 19 ± 13 hours. Abrupt closure tended to occur in patients with unstable or postinfarction angina, in those who recently received thrombolytic therapy, and in de novo narrowings.

In the postinfarction period after treatment with tissue plasminogen activator there is a high incidence of abrupt closure after balloon angioplasty.[7] The mechanism is presumed to be in situ thrombosis caused by exaggerated platelet activation at the exposed unstable site. In our total series of 270 patients, 13 had an acute infarction treated with thrombolytic therapy, and 10 with tissue plasminogen activator. Of these 10 patients, 4 had abrupt closure. The angiographic appearance of the abrupt closure and its response to balloon angioplasty suggest a thrombotic mechanism. DCA may expose media/adventitia (Figure 2) or lipid from a lipid-rich plaque, both of which are highly thrombogenic. Tissue plasminogen activator may further sensitize this thrombogenic milieu causing increased platelet activation and more frequent thrombotic complications.

Late abrupt closure after angiographically successful DCA is, in fact, unusual. However, it occurs with a frequency not dissimilar to that of balloon angioplasty. Because abrupt closure tended to occur after patients left the catheterization laboratory, they should be monitored carefully even if the procedure is successful and uncomplicated. In addition, it may be prudent to either avoid DCA in the postinfarction/postthrombolytic setting or treat these patients more vigorously with prolonged sys-

TABLE II Clinical and Angiographic Characteristics of Six Patients Who Developed Abrupt Closure Out of the Cardiac Catheterization Laboratory After Angiographically Successful Directional Coronary Atherectomy

Pt.	Age (yr) & Sex	Vessel	ACC/AHA Lesion Class	NYHA Angina Class	tPA Days Before	LV Function	Device Sizes	Interval from DCA to Closure (hours)	DCA Stenosis %	
									Before	After
1	M54	Right	C	II	42	+	6Fr	48	100	25
2	M57	LAD	C	III	7	0	6Fr	12	80	20
3	F62	LAD	B	II	?	0	5Fr	12	85	25
4	M67	LAD	A	II	16	+	5Fr	16	85	20
5	F68	Right	A	IV	5	0	7Fr	12	75	28
6	F76	LAD	B	IV	?	0	6Fr 5Fr	12	70	30

ACC/AHA = American College of Cardiology/American Heart Association; DCA = directional coronary atherectomy; LAD = left anterior descending; LV = left ventricular; NYHA = New York Heart Association; tPA = tissue plasminogen activator.

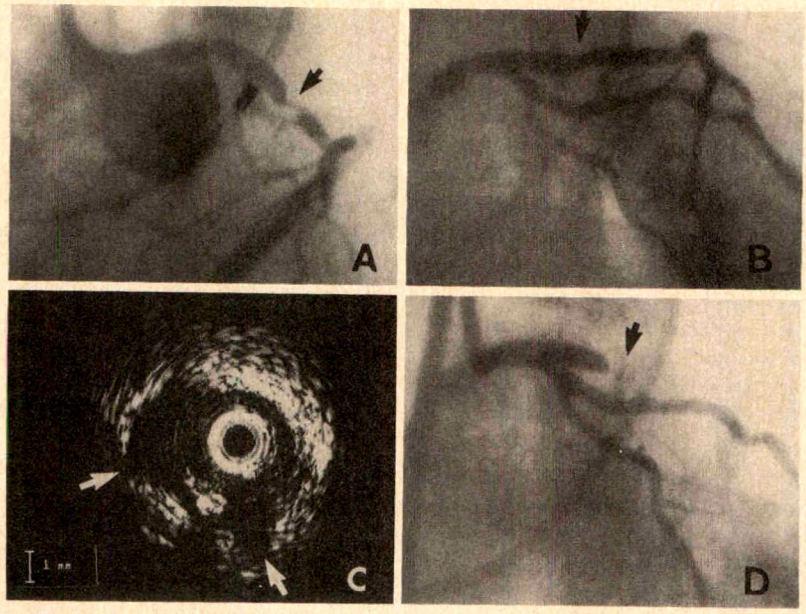


FIGURE 2. ***Panels A, B, C and D*** **from patient no. 4 with left anterior descending coronary artery disease treated with directional coronary atherectomy (DCA). There is 85% narrowing before DCA** ***(A, arrow)*****, which improved to 20% without dissection or thrombus after DCA** ***(B, arrow)*****. Intravascular ultrasound after DCA** ***(C)*** **showed deep atherectomy cuts into media and adventitia** ***(white arrows)*****. Sixteen hours later patient complained of chest pain, and electrocardiogram showed acute anterior lead changes. Coronary arteriography showed acute closure at DCA site** ***(D, arrow)*****.**

temic anticoagulation or intracoronary urokinase, or both.

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Acute Myocardial Infarction and Day of the Week

David R. Thompson, PhD, Jurgen E. F. Pohl, FRCP, and Terence W. Sutton, PhD

Several studies investigated the relation between the incidence of acute myocardial infarction and the days of the week.[1-5] Most of these studies concerned mortality[3-5] and found that the incidence is highest on Monday and Saturday. Furthermore, the World Health Organization Regional Office for Europe project of the Myocardial Infarction Community Registers[2] also found the peak incidence of heart attacks on these days. There was significant deviation from the uniform distribution in only 1 of the 19 centers involved, although when the figures from all the centers were combined (n = 8,511), a statistically significant but small difference in the distribution from the uniform was seen. We studied the relation between the frequency of occurrence of myocardial infarction and the days of the week in 2,254 patients admitted to a coronary care unit during a 10-year period.

Patients are admitted to the coronary care unit of Leicester General Hospital by the emergency ambulance service. The average delay between reporting onset of symptoms and admission to the unit is about 30 minutes. The 2 main coronary care units admit patients 7 days a week from all parts of the city of Leicester and its surroundings. The number of patients admitted at the hospital is approximately 50% of the total of those with suspected acute myocardial infarction, without geographic, sex or age bias. Since the inception of the coronary care unit in 1976 we have kept accurate records of patient characteristics, documenting the date and time of onset of chest pain, and admission to and discharge from the unit, together with electrocardiographic and cardiac enzyme changes, complications and therapy. We examined the records of all patients admitted to the unit between January 1, 1979, and December 31, 1988. Of 8,881 admissions, 3,239 (36%) had an acute myocardial infarction, according to the Minnesota code criteria. Nine hundred eighty-five patients were excluded from the study on the basis of absence of pain, admission to the unit >24 hours after onset of symptoms (a rare reason for exclusion), or insufficient documentation on admission due to uncertainty, language difficulties or collapsed state. Time of onset of chest pain was taken to the nearest hour.

All data were statistically analyzed by chi-square tests of uniformity. There was a statistically significant difference from the uniform distribution. Table I shows an excess on Monday and a relative deficit on Tuesday. When the data were divided into subgroups (men, women, aged < or ≥65 years), only men of all ages (n = 1,743), and women aged <65 years (n = 244) had statistically significant results. Men had a peak occurrence on Monday and a minimum on Tuesday. Although there was a relatively high peak on Saturday, this was not statistically significant. Women aged <65 years had a peak occurrence on Thursday and a minimum on Saturday. To take account of the fact that most women retire at 60 years, the data were also analyzed for women aged <60 years. The results showed minimal occurrences on Wednesday and Saturday (χ^2 = 18.16; p <0.05).

We do not have data on employment at the time of admission, but believe it is acceptable to assume that men aged ≥65 years and women aged ≥60 are retired.

Studies of the occurrence of heart attacks in West Germany[1] and throughout Western Europe[2] reported an excess of their occurrence on Mondays and, to a lesser extent, Saturdays, particularly in men. Massing and Angermeyer[5] found support for their prediction that based on work in industrial societies being organized according to a defined weekly pattern, there would be an excess of deaths from myocardial infarction on these 2 days. Mondays and Saturdays are days on which people must adjust to a new phase, whether of work or of leisure. The stress of returning to work may induce a heart attack. Our finding of a minimal occurrence on Tuesday was not reported in other studies, and the reason for this is unclear.

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TABLE I Relation of the Frequency of Occurrence of Acute Myocardial Infarction to Days of Week

	Age Group	Mon	Tue	Wed	Thu	Fri	Sat	Sun	Total	χ^2	p Value
Men	<65	187	141	157	155	142	175	166	1,123	10.63	>0.05
	≥65	93	65	101	94	89	96	82	620	9.69	>0.05
Total		280*	206*	258	249	231	271	248	1,743	14.86	<0.05
Women	<65	39	32	27	51*	33	19*	43	244	19.17	<0.01
	≥65	44	39	39	30	44	47	24	267	10.9	>0.05
Total		83	71	66	81	77	66	67	511	4.36	>0.05
Grand total		363*	277*	324	330	308	337	315	2,254	13.18	<0.05

*Statistically significant contributions at the 0.05 level.

The pattern for women was very similar to that reported by Döring and Loddenkemper,[1] although we found that a reanalysis of their data for women aged <60 years was not statistically significant ($\chi^2 = 8.78$; $p > 0.05$). The reasons for the different patterns found between men and women are unknown and merit further research.

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Effectiveness of Indapamide Versus Enalapril as Second-Step Therapy of Systemic Hypertension

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Angiotensin-converting enzyme inhibitors are recommended and increasingly used as the initial drug for the treatment of hypertension.[1,2] When hypertension is not fully controlled by an initial dose of an agent of this drug class, it is unclear whether upward titration is as effective as adding a second drug. This issue was examined by studying patients unresponsive to an initial dose of enalapril. We compared the effectiveness of the upward titration of enalapril with that of adding the diuretic indapamide. Because there are data to suggest a flat dose-response curve for enalapril >10 to 20 mg/day,[3,4] patients uncontrolled with 5 mg/day, a dose presumably near the steep portion of the curve, were studied.

This was a prospective randomized, double-blind, placebo-controlled parallel study of indapamide as add-on therapy in comparison with upward titration of enalapril in mild to moderate hypertension. Patients remaining hypertensive after receiving enalapril (5 mg/day) were randomized to supplemental treatment with an additional 5 mg of enalapril, indapamide (2.5 mg/day) or placebo.

Ambulatory patients with a history of hypertension were recruited by 5 investigators who used a common protocol. The patients were men and women aged between 21 and 75 years who were free of clinically evident concomitant disease. Patients were also excluded for obesity or use of other drug treatments including insulin, lithium and nonsteroidal antiinflammatory drugs.

After written consent was signed, patients discontinued taking any prior antihypertensive drug treatment. Placebo capsules were given in open fashion during a 3-week washout period. At the end of the placebo period, patients whose supine diastolic blood pressure was between 95 and 115 mg Hg were given enalapril in a dose of 5 mg/day. Those with higher or lower blood pressure were removed from the study. If diastolic blood pressure remained between 95 and 120 mm Hg after 2 weeks of enalapril, the patient qualified for randomization. Randomization separated patients into 3 add-on treatment regimens: (1) indapamide (2.5 mg/day), (2) enalapril (5 mg/day), or (3) matching placebo. All patients continued to take the open treatment of 5 mg of enalapril daily during the double-blind phase.

Visits were weekly before randomization and monthly after it. At each visit vital signs and weight were recorded before the daily dose of medication. Blood was drawn for a complete cell count and multisystem chemistry testing at the screening visit, at the randomization visit and at each of the 4 monthly double-blind visits. Measurements recorded at the randomization visit (i.e., after 2 weeks of enalapril therapy) served as the baseline.

Adherence to the drug regimen was assessed by pill counts. Patients not taking 80% of their medication on 2 consecutive visits were withdrawn from the study. No dietary advice was given. Blood testing was performed by a central laboratory, namely, Scicor Laboratory of Indianapolis, Indiana.

With regard to statistical methods, mean changes in blood pressure among the treatment regimens at 4, 8, 12 and 16 weeks, and the last visit were compared using 2-way analysis of variance. The "last visit" designation represents the last study visit that patients who received double-blind treatment were seen, whether or not they completed the 16-week protocol. Changes in blood chemistry from baseline were analyzed within each treatment group by Student's paired t test at each of the double-blind visits. Only the 16-week laboratory values are reported. Statistical significance was taken as $p < 0.05$ (2-tailed).

Informed consent was signed by 187 patients. Twenty-seven (14%) were withdrawn from the study during the 3-week washout period (23 patients because of blood pressures not meeting protocol requirements and 4 pa-

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TABLE I Clinical Features of Protocol-Eligible Patients

	Placebo	Enalapril	Indapamide
No. of pts.	39	30	29
Women/men	18/21	15/15	14/15
Black, hispanic, white	9, 1, 29	5, 6, 19	4, 2, 23
Age (yr)	54 ± 11*	57 ± 12	55 ± 10
Weight (lbs)	192 ± 43*	176 ± 29	182 ± 32
Body mass index	29.7 ± 5.9*	27.3 ± 3.5	27.8 ± 3.5
Supine blood pressure			
Systolic (mm Hg)	156 ± 18*	157 ± 14	154 ± 20
Diastolic (mm Hg)	101 ± 5*	101 ± 5	100 ± 5

*Mean ± standard deviation.
Hispanics were unevenly distributed among the groups.

tients for other reasons). After the 3-week washout period, 160 patients qualified with a diastolic blood pressure between 95 and 115 mm Hg and were entered into a 2-week treatment period with enalapril (5 mg/day). At the end of the 2-week period, 32 patients (20%) were not randomized because of a diastolic blood pressure <95 mm Hg and 5 (3%) for other reasons. Thus, 123 patients were randomized to the 16-week double-blind add-on treatment period. However, 18 patients with diastolic blood pressure <95 mm Hg were erroneously randomized. These subjects were eliminated from the efficacy analysis because their baseline blood pressure would be too low to judge response. Seven of the properly randomized patients failed to complete 21 days of double-blind treatment and were excluded from the primary analysis. Hence, 98 subjects were properly evaluable for effects of the double-blind treatment on blood pressure and blood chemistry. The demographic features of these 98 patients are displayed in Table I. All 123 randomized patients were included in the analysis of adverse experiences.

Group mean blood pressures in the supine and standing positions at the end of washout, baseline, the 4 monthly double-blind visits, and the last visit are depicted in Figures 1 and 2. Diastolic blood pressure decreased significantly from baseline in both the supine and standing positions at each visit in all 3 treatment groups. However, the decrease in the group taking combination therapy was significantly greater at all visits ($p < 0.01$) than in the 2 groups on monotherapy (−12, −3 and −3 mm Hg at the last visit in the supine position in the combination, enalapril 5 mg, and enalapril 10 mg groups, respectively). Systolic blood pressure in both positions decreased significantly and consistently only with the combination regimen (−18 mm Hg in the supine position at the last visit). Systolic blood pressure did not decrease significantly from baseline in the enalapril 5 mg group. In the enalapril 10 mg group, systolic blood pressure decreased significantly from baseline only at week 8 (both supine and standing positions) and week 12 (supine position only). Changes from baseline in blood pressure differed significantly between the 5 and 10 mg dose of enalapril only at week 16 and the last visit when the 10 mg dose prevented a late increase in standing systolic pressure. Figure 3 depicts the percentage of patients with supine diastolic pressure <90 mm Hg at the double-blind visits.

Heart rate changed minimally, except at week 12 in the enalapril 10 mg group when it increased by 5 beats/min ($p < 0.05$ vs the comparison groups). Respirations were unchanged with all 3 regimens. Body weight decreased by 2 to 4 pounds ($p < 0.05$) at all visits in the combination group, but the changes from baseline were similar among groups (Figure 4).

Baseline values of selected blood chemistries and changes from baseline at week 16 are tabulated in Table II. Serum potassium decreased significantly in the com-

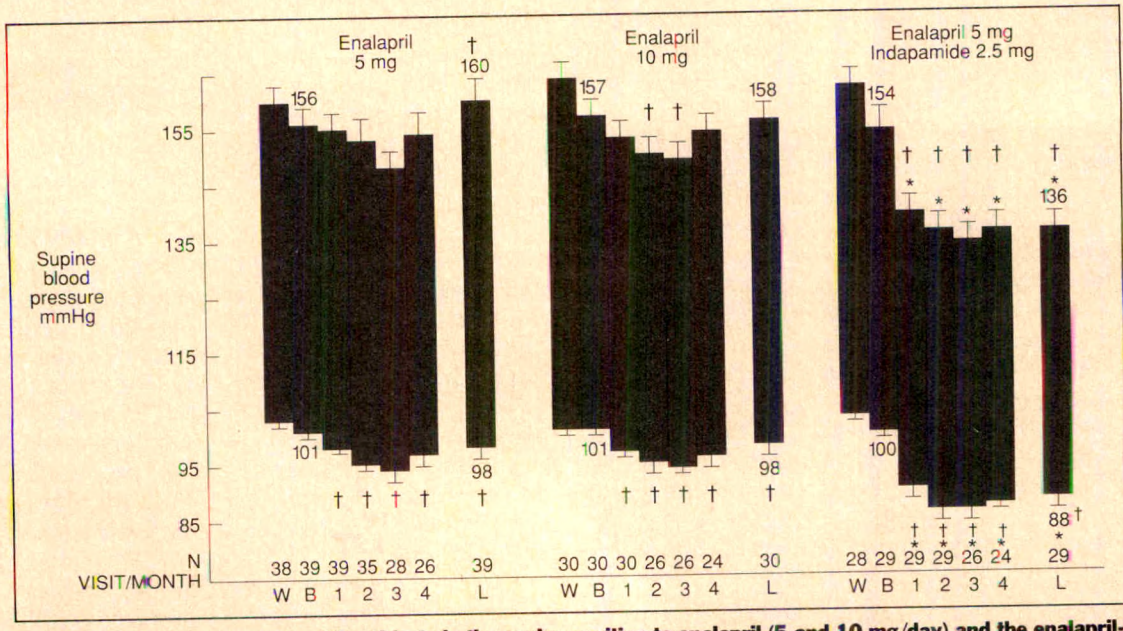


FIGURE 1. Blood pressure response with subjects in the supine position to enalapril (5 and 10 mg/day) and the enalapril-indapamide combination drug regimen. Blood pressure was significantly lower at all the double-blind visits with the combination regimen ($p < 0.01$). Blood pressure response to 10 mg of enalapril did not differ from the 5 mg dose. *Bars* represent mean blood pressure ± standard error of the mean. B = baseline; L = last visit; W = end of washout; *$p < 0.01$ versus both enalapril doses; †$p < 0.05$ or better versus baseline.

bination group, but the group mean value remained within the normal range. Five of 22 patients (23%) in the combination group had serum potassium levels <3.5 mEq/liter at the sixteenth week of treatment. The lowest value recorded was 3.0 mEq/liter in the combination group. Uric acid increased significantly with the combination regimen. Total cholesterol increased 4.5% with combination therapy, but this change did not reach statistical significance. Uric acid and urea nitrogen increased significantly in the enalapril 10 mg group. Serum potassium was unchanged by enalapril therapy. Symptomatic side effects were similar in the 3 treatment groups.

This multicenter protocol compared the effectiveness of different strategies for the second-step treatment of hypertension. Patients remaining hypertensive after treatment with enalapril (5 mg/day) received a higher dose of enalapril or the addition of a diuretic (i.e., indapamide). The addition of indapamide proved more effective in reducing blood pressure.

The major effect of the increased dose of enalapril was to prevent the late rise in systolic blood pressure at week 16 and the last visit seen in the enalapril 5 mg group (Figure 2). Because of further evidence of a tendency to escape from control by low-dose therapy, 8 patients were removed from the 5 mg group due to inadequate control, whereas only 3 and 2 patients were removed for this reason from the 10 mg enalapril and the combination groups, respectively.

The importance of a placebo control group in study design is highlighted in this trial. The 29% response rate in the enalapril 10 mg group (Figure 3, last visit) implies a notable effect of the increased dose. However, the 23% response rate in the placebo group changes the interpretation. The similar response rate in the 2 monotherapy groups suggests that a late response to the initial 5 mg

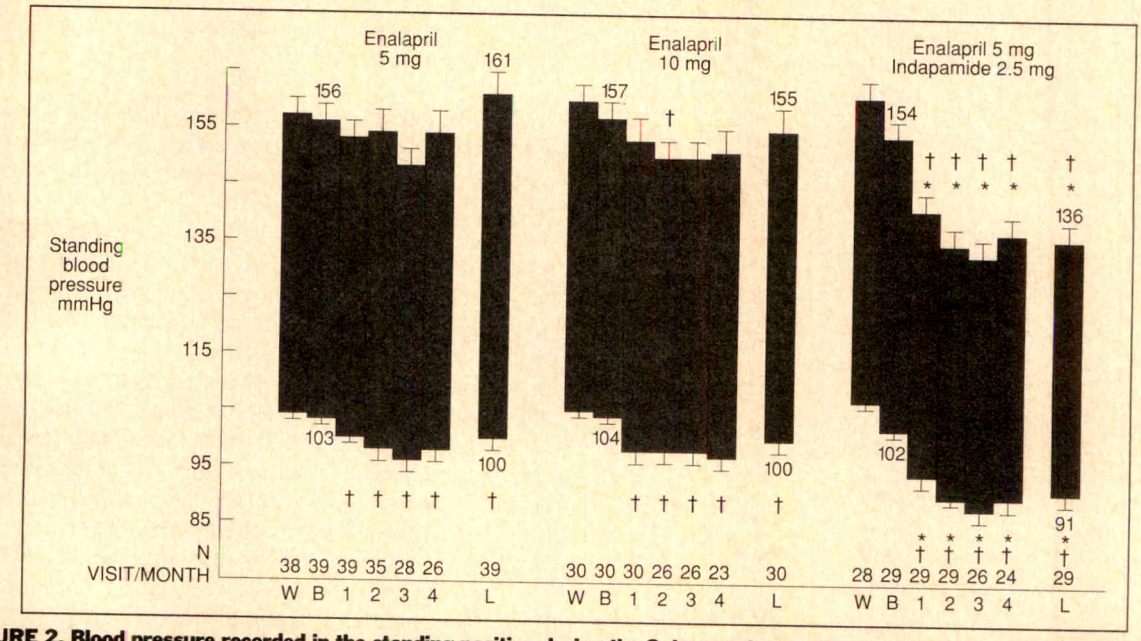


FIGURE 2. Blood pressure recorded in the standing position during the 3 drug regimens. Blood pressure was significantly lower at all double-blind visits with the combination of drugs ($p < 0.01$). Ten mg/day of enalapril was superior to 5 mg/day only at week 16 and the last visit for the systolic measurement ($p < 0.05$). Abbreviations and symbols as in Figure 1.

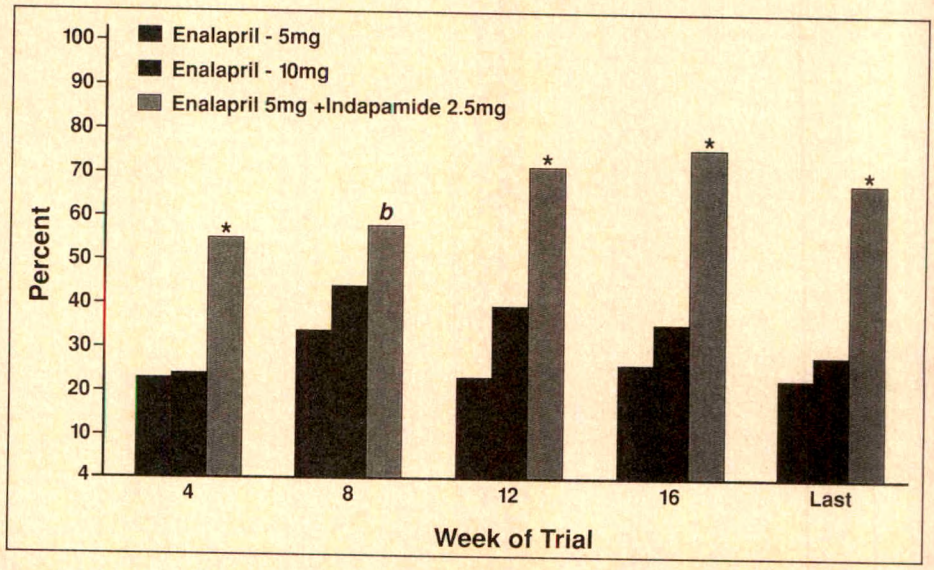


FIGURE 3. Percentage of subjects in each of the 3 treatment regimens with supine diastolic blood pressure <90 mm Hg at the various weeks of treatment. b = p = 0.06 versus enalapril (5 mg); *p <0.02 versus both doses of enalapril.

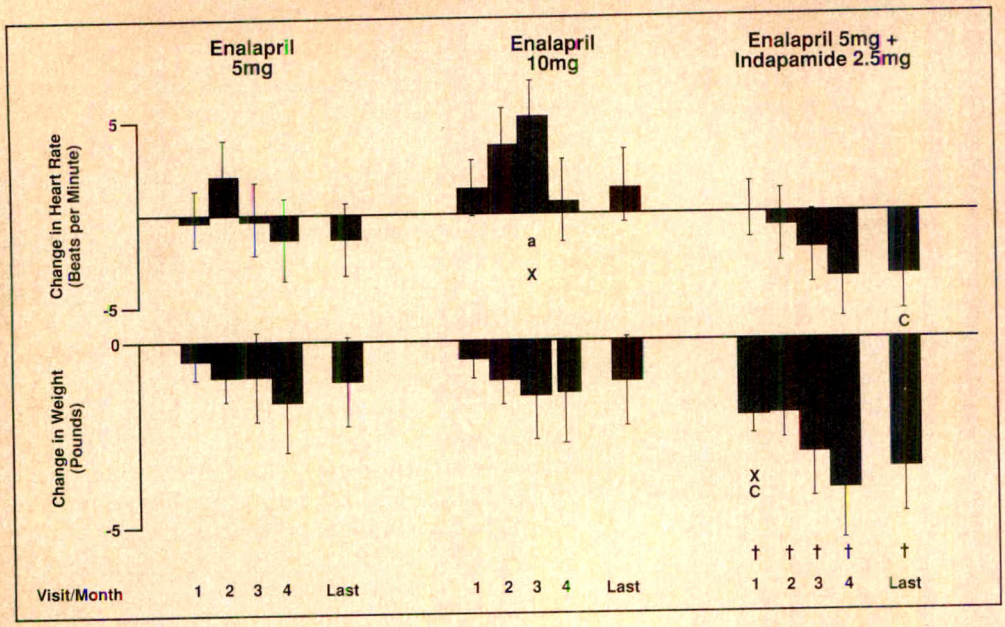


FIGURE 4. Changes in heart rate and weight during the 4-month, double-blind phase in the 3 treatment groups. †p <0.05 or better versus baseline; [a]p <0.01 versus the combination regimen; [x]p <0.05 versus enalapril (5 mg); [c]p <0.05 versus enalapril (10 mg).

TABLE II Selected Blood Chemistry Values at Baseline and Changes at Week 16 by Treatment Group

	Baseline Mean	Change at Week 16	p Value vs Baseline
Urea nitrogen (mg/dl)			
Placebo	15.5	−0.3	NS
Enalapril	14.4	1.6	0.03
Indapamide	13.4	1.2	NS
Uric acid (mg/dl)			
Placebo	4.9	0.3	NS
Enalapril	5.1	0.8	0.01
Indapamide	5.0	1.3	0.01
Potassium (mEq/liter)			
Placebo	4.3	−0.05	NS
Enalapril	4.4	−0.02	NS
Indapamide	4.5	−0.53	0.01
Glucose (mg/dl)			
Placebo	107	−2.7	NS
Enalapril	103	4.5	NS
Indapamide	100	5.3	NS
Total cholesterol (mg/dl)			
Placebo	225	5	NS
Enalapril	217	−3	NS
Indapamide	217	10	0.08
Triglycerides (mg/dl)			
Placebo	138	−4	NS
Enalapril	173	−18	NS
Indapamide	170	7	NS

NS = not significant.

dose of enalapril or a placebo effect accounted for the additional reduction in diastolic blood pressure in the double-blind phase. Perhaps the 2 weeks of single-blind therapy was too short an interval to judge the full effect of enalapril. Enalapril (10 mg/day) might have produced a greater antihypertensive effect if given in a divided daily schedule. We selected a once-daily regimen for its convenience of administration.

The combination regimen produced a mild degree of hypokalemia despite the expected potassium-sparing property of enalapril. The lowest potassium level recorded was 3.0 mEq/liter; thus, few patients would require corrective measures. Total cholesterol increased nonsignificantly by 10 mg/dl (Table II). We did not obtain cholesterol fractionation to ascertain which lipoprotein components were raised. There are reports of increases in high-density lipoprotein cholesterol with indapamide.[5,6] Thus, it is unclear whether this lipid modification represents an adverse effect. Using Framingham estimates, the combination regimen would lower 6-year coronary probability by 15% in a 55-year-old man, taking into account both cholesterol and systolic blood pressure changes.[7] The 10 mg enalapril dose would produce no change from baseline in coronary probability since neither systolic blood pressure nor other risk factors changed significantly. In addition, the pressure-mediated complications of hypertension, namely stroke and heart failure, would be more favorably impacted by the combination regimen.

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Efficacy of Once-Daily Felodipine Monotherapy in Systemic Hypertension

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Felodipine is a dihydropyridine calcium antagonist that, in therapeutic concentrations, causes arteriolar dilatation through a selective action on smooth muscle in the resistance vessels.[1] It lowers systemic vascular resistance, produces a substantial decrease in blood pressure (BP) and an increase in cardiac output. Felodipine, in an extended release tablet formulation, produced a sustained 24-hour antihypertensive effect in the initial studies of patients with essential hypertension.[2,3] This drug is available for prescription in about 20 countries in the world and it has recently been approved by the Food and Drug Administration in the USA. This study assesses the 24-hour efficacy of felodipine, administered as once-daily monotherapy in mild to moderate hypertension.

Nineteen Chinese patients (8 men, 11 women) aged 26 to 60 years (mean 48) with essential hypertension of World Health Organization grades I to II were included in the study. Patients were enrolled after 3 separate clinic visits showing diastolic BP >95 mm Hg with use of a mercury sphygmomanometer. Laboratory examination included urinalysis, electrocardiography, echocardiography and studies to exclude secondary hypertension. The study was of a single-blind design with placebo run-in. All patients received felodipine, with dose titration from 5 to 20 mg/day. Ambulatory BP monitoring was performed twice in each patient. Baseline ambulatory BP monitoring was obtained after the 2-week placebo run-in period, after 4 to 5 weeks of active felodipine therapy, or after the clinic visit at which an optimal dose that controlled BP (diastolic BP <90 mm Hg) was given.

The automated portable model 90202 BP monitor (Space Labs Inc., Redmond, Washington) was used. This portable device used a standard cuff which was placed around the left upper arm and inflated at regular preset intervals (every 30 minutes during the daytime period, i.e., 6 A.M. to 6 P.M. and every hour during the nighttime period, i.e., 6 P.M. to 6 A.M. through the whole day). Systolic and diastolic BPs were estimated by the oscillometric method. At the end of the 24-hour monitoring period, the collected data of BP and heart rate were unloaded from the memory into a microcomputer for further analysis. Physiologic testing including BP and heart rate at supine rest for 10 minutes, sitting for 5 minutes and standing for 3 minutes were performed before and after therapy.

Blood samples for felodipine concentration determination were taken before administration of the drug (9 A.M.) and at 2, 4, 6 and 24 hours after the last dose of felodipine. After the first blood sample was obtained, the second ambulatory BP monitoring was begun immediately, and the last maintenance dose of felodipine was administered. Plasma samples were kept frozen at −20°C until analysis.[4]

Before and after therapy, BP and heart rate differences were tested by using the Wilcoxon signed rank test. A p value <0.05 was considered significant. Recordings that showed an inconsistent increase or decrease in systolic or diastolic BP of >50 mm Hg without changes in heart rate, and a calculated pulse pressure of <10 mm Hg were deleted before analysis.[5,6] The day and night BP reduction rates were calculated according to the following formula: systolic BP reduction % = [systolic BP (before treatment) − systolic BP (after treatment)]/systolic BP (before treatment) × 100.

Nineteen patients with mild to moderate hypertension (World Health Organization grades I to II) completed the study. The mean 24-hour systolic/diastolic BP was significantly decreased compared with that at the baseline (132 ± 9/87 ± 5 vs 157 ± 9/102 ± 7 mm Hg; p <0.0005/0.0005) (Table I). The average optimal dose of felodipine was 12 ± 2 mg (range 10 to 20) after a dose titration period of 5 weeks (range 3 to 8) of treatment. Mean daytime BP decreased from 159 ± 9/103 ± 6 to 133 ± 9/87 ± 5 mm Hg (p <0.0005/0.0005), and the nighttime BP from 152 ± 12/98 ± 9 to 130 ± 10/85 ± 7 mm Hg (p <0.0005/0.0005). Figure 1 shows the consecutive hourly systolic and diastolic BP. Before felodipine treatment, the circadian variation showed a peak BP at 10 A.M. and a nadir at 2 A.M. After treatment, significant BP reduction (p <0.05/0.05) was seen throughout the 24-hour period, except diastolic BP recorded at 12 P.M. The circadian rhythm of BP was preserved as indicated

TABLE I Mean (±SD) Ambulatory Blood Pressure (mm Hg) and Heart Rate (beats/min) in 19 Patients Before and After Felodipine Treatment

	Treatment	
	Before	After
Blood pressure		
Systolic*		
24-hour	157 ± 9	132 ± 9
Daytime	159 ± 9	133 ± 9
Nighttime	152 ± 12	130 ± 10
Diastolic*		
24-hour	102 ± 7	87 ± 5
Daytime	103 ± 6	87 ± 5
Nighttime	98 ± 9	85 ± 7
Heart rate†		
24-hour	76 ± 11	82 ± 9
Daytime	78 ± 11	84 ± 9
Nighttime‡	73 ± 11	77 ± 10

*All pre- to posttreatment difference, p <0.0005.
†All pre- to posttreatment difference, p <0.005.
‡Not significant.

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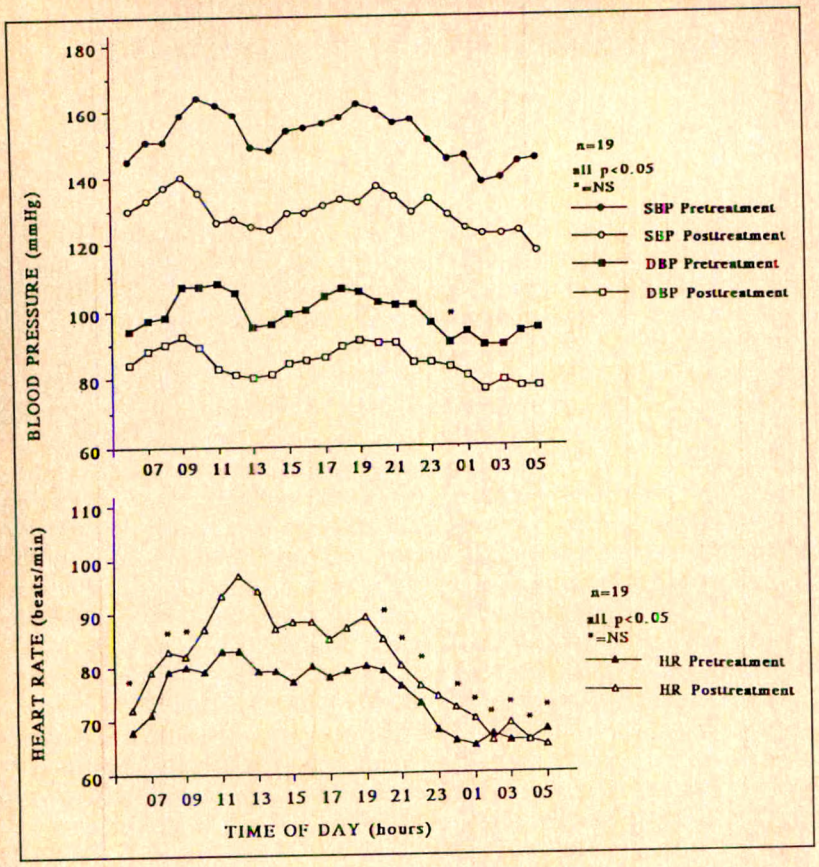


FIGURE 1. Circardian variations in systolic (SBP) and diastolic (DBP) blood pressures and heart rate (HR) before and after felodipine treatment in 19 patients. NS = not significant.

TABLE II Mean (±SD) Systolic/Diastolic Blood Pressure (mm Hg) and Heart Rate (beats/min) During Physiologic Tests in 19 Patients Before and After Felodipine Treatment

	Treatment	
	Before	After
Blood pressure*		
Supine	162 ± 12/102 ± 7	138 ± 16/90 ± 9
Standing	168 ± 13/111 ± 9	138 ± 13/94 ± 9
Sitting	167 ± 13/111 ± 7	141 ± 15/95 ± 9
Heart rate†		
Supine	69 ± 10	73 ± 10
Standing	77 ± 11	84 ± 2
Sitting	74 ± 12	79 ± 11

*All differences before and after treatment, $p < 0.0005$.
†All differences before and after treatment, $p < 0.05$.

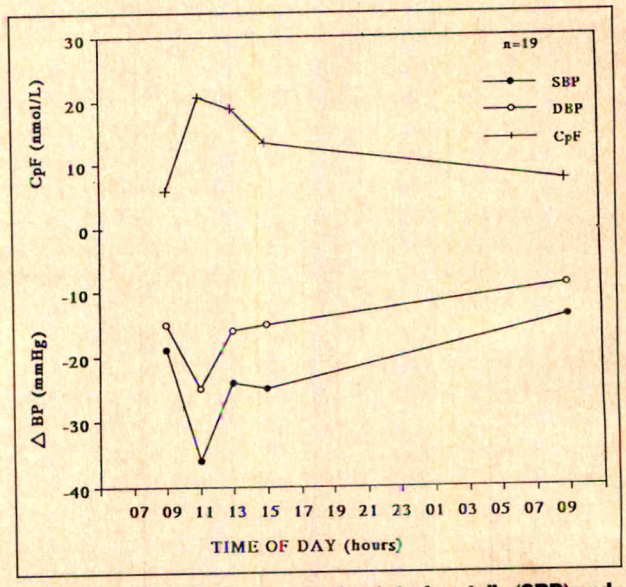


FIGURE 2. Time profile of reduction (Δ) of systolic (SBP) and diastolic (DBP) blood pressures and plasma concentration of felodipine (CpF) after felodipine therapy.

by similar BP standard deviations (15 ± 4/11 ± 3 vs 13 ± 2/11 ± 1 mm Hg). The mean 24-hour heart rate increased from 76 to 82 beats/min ($p < 0.005$) and daytime heart rate increased by 6 beats/min ($p < 0.005$) with therapy. However, no significant heart rate changes were seen during nighttime with therapy. The consecutive hourly heart rate showed a significant ($p < 0.05$) increase from baseline in 12 of the 24 time points (Figure 1). The systolic BP reduction rates to after treatment were 16.0 ± 5.0% during the day and 14.4 ± 6.3% during the night. Diastolic BP reduction rates were 15.3 ± 6.0% during the day and 13.7 ± 7% during the night. Physiologic testing was completed in all patients (Table II). Both systolic and diastolic BPs in supine, sitting and standing positions were significantly reduced after treatment ($p < 0.0005$). No postural hypotension was found in either the sitting or standing position. A significant ($p < 0.05$) increase in heart rate was also noted during therapy.

At steady state, after the last dose of felodipine intake, the maximum and minimum levels of felodipine

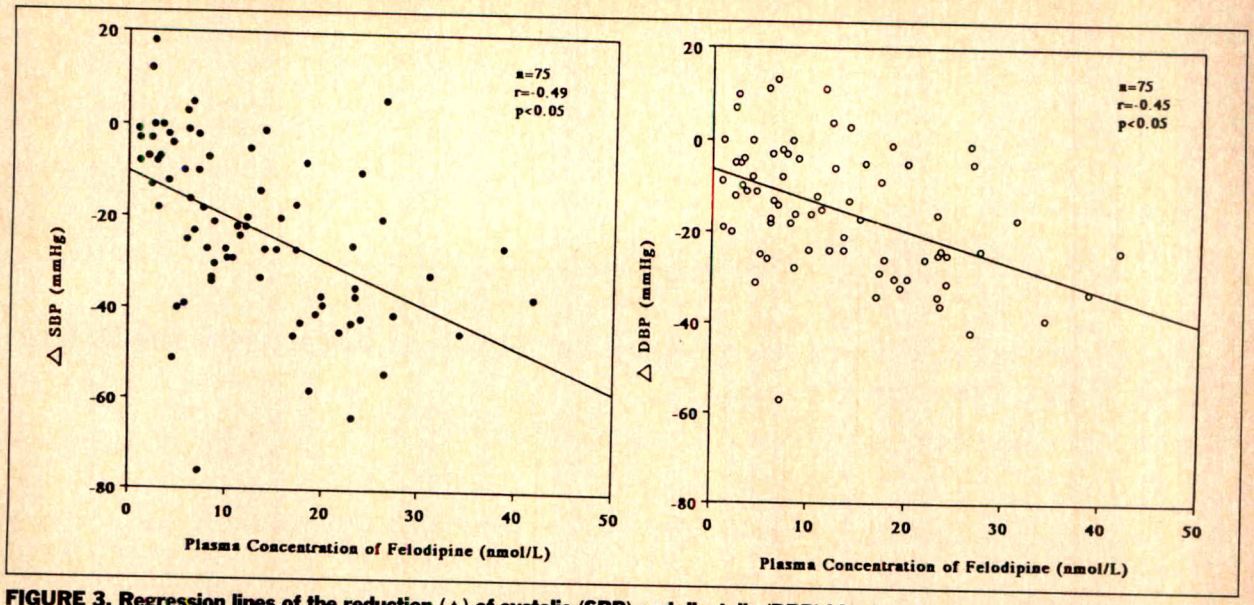


FIGURE 3. Regression lines of the reduction (Δ) of systolic (SBP) and diastolic (DBP) blood pressures versus plasma concentration of felodipine at steady state.

plasma concentration were 20.5 ± 9.9 and 5.8 ± 3.7 nmol/liter, respectively. The maximum and minimum levels occurred at 2 and 24 hours after each dose, respectively. The maximum to minimum ratio was 3.5 (Figure 2). The systolic and diastolic BP reductions were similar to the felodipine blood levels (Figure 2). Complete data of plasma concentrations were available in 15 patients. The reduction in systolic and diastolic BP after treatment compared with baseline values was significantly correlated with plasma concentration of felodipine ($r = -0.49$, $p < 0.05$; $r = -0.45$, $p < 0.05$, respectively). The regression lines for these relations are depicted in Figure 3. Adverse events were reported in 3 patients; 2 patients had palpitation and 1 had pedal edema. The events were mild and transient.

The newly developed extended-release formulation of felodipine has provided once-daily therapy for control of essential hypertension.[2,7] The present study has demonstrated that felodipine can effectively and significantly reduce BP throughout the 24-hour period, while diurnal variation was preserved. However, our study showed effective BP reduction throughout the early morning; the weak BP control in the morning reported by Porcellati et al[2] was not found in this study. In our view, this discrepancy may be due to the relatively larger dose of felodipine and the longer duration of therapy used in our study.

BP reduction was more pronounced during the daytime period than during the nighttime period in this study. This is in agreement with previous studies.[2,3] Moreover, it indicated that once-daily administration of felodipine provided good control of BP during the apparent high-risk acceleration phase of circadian BP cycle. We suggested that control of BP, particularly during the morning BP surge, may reduce mobility and mortality of cardiovascular events.

Correlation between plasma concentration and reduction in BP was not detected in some studies.[8,9] However, correlation after a single dose,[10] and during long-term treatment, was confirmed by other investigators.[9,10] Edgar et al[11] used a nonlinear model to establish the correlation between plasma concentration and effect on diastolic BP. They found that the therapeutic range was 2.5 to 30 nmol/liter. The therapeutic range of approximately 2.0 to 20 nmol/liter was reported by Blychert et al.[7] Our study showed a similar therapeutic range of felodipine (5.8 to 20.5 nmol/liter). We also found that there was a significant correlation between plasma concentration of felodipine and its antihypertensive effect; this was also in agreement with previous reports.[7,11] The plasma concentration of felodipine versus time curve after the last dose was relatively "flat." The absence of sudden peaks in blood levels of felodipine may account for the few adverse events experienced by the patients in this study.

In conclusion, felodipine administered as once-daily monotherapy provides effective BP control over a 24-hour period in Chinese patients. There was a close relation between plasma concentration of felodipine and its antihypertensive effect.

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Transesophageal Echocardiography for Study of Bioprostheses in the Aortic Valve Position

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Transesophageal echocardiography is a relatively new imaging modality with unequivocal advantage over precordial echocardiography in a significant number of conditions.[1–3] The importance of transesophageal echocardiography in the assessment of aortic valve disease (native or prosthetic) has not been clearly shown. There is some evidence from anecdotal case reports[4,5] and small series of patients that it may be superior to transthoracic imaging.[6] The present study was undertaken to evaluate the use of transesophageal echocardiography in the setting of bioprosthetic aortic valve disease and to define the clinical situations in which its use is superior to the precordial approach.

Between July 1987 and July 1990, 33 patients (19 men and 14 women, mean age 61 ± 13 years) were studied by transesophageal echocardiography for suspected bioprosthetic aortic valve disease, and the recordings were reviewed retrospectively. The indication for transesophageal echocardiography was based on a strong clinical suspicion of aortic valve abnormalities, yet with a normal aortic valve by the transthoracic approach, or when there was a suspicion, but not definite, of an abnormality of the aortic valve on the transthoracic study. Sixteen patients were referred for suspected infective endocarditis, 12 for aortic prosthesis assessment, and 5 for suspected prosthetic dysfunction. Twenty-seven patients were inpatients and 6 were ambulatory. Thirteen patients underwent subsequent cardiac surgery.

All ultrasound recordings were obtained using a Hewlett-Packard ultrasonograph (Model Sonos 500, Andover, Massachusetts) with a 5 MHz single-plane transducer mounted at the tip of a 14 mm adult gastroscope (Model 21362A, HP echoscope). All studies were performed in awake patients. All patients fasted for ≥6 hours. Premedication with Midazolam (1 to 3 mg) was routinely performed. Local pharyngeal anesthesia was achieved with lidocaine (10% spray and 2% gel). The echoscope was introduced into the esophagus with the transducer facing anteriorly. Tomographic planes were obtained in the usual fashion by translating and rotating the echoscope within the esophagus while observing the ultrasonic image for reference.[3] To obtain the best views of the aortic valve and annulus, a modified 4-chamber view was obtained. Then, the probe was slightly pulled back until the left ventricular outflow tract and aortic valve leaflets were visualized. At this point, a smaller ultrasound depth (usually 8 cm) was used. Continuous imaging was recorded on one half inch videotape. All studies were well-tolerated, with no complications reported. All patients underwent a transthoracic study before the transesophageal study for comparison, usually within 24 hours and no longer than 72. All transesophageal recordings were read without knowledge of clinical, surgical and transthoracic findings.

A vegetation was defined as a localized mobile mass of soft echoes contiguous with a prosthetic valve leaflet (Figure 1). An abscess was defined as an abnormal pul-

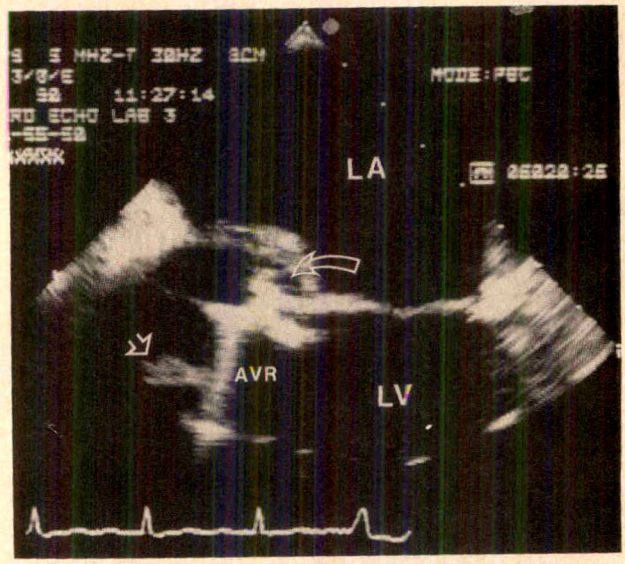


FIGURE 1. Seventy-two-year old patient with bioprosthetic aortic valve and clinical diagnosis of infectious endocarditis. Transesophageal echocardiogram shows small echolucent perivalvular area in left coronary sinus interpreted as small abscess *(curved open arrow)*, and mobile mass attached to aortic prosthesis *(straight open arrow)*. Surgery confirmed presence of small abscess and torn leaflet with vegetation. These findings were not seen by transthoracic echocardiogram. AVR = aortic valve replacement; LA = left atrium; LV = left ventricle.

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satile echolucent area within the perivalvular tissue without communication with the circulation (Figure 1).

In 23 patients (70%), transthoracic and transesophageal studies showed identical results. In 8 patients (24%), transesophageal echocardiography gave more information than did precordial echocardiography. Two of these 8 patients had confirmed infective endocarditis by surgery. One of these 2 patients had, in addition to a vegetation, severe aortic regurgitation and a left ventricular-right atrial fistula also confirmed at surgery (Figure 2); the other had a para-annular abscess related to the right coronary sinus, and a torn prosthetic leaflet. Two patients had torn leaflets not diagnosed by transthoracic views and subsequently confirmed by surgery. Three of the latter 4 patients had no catheterization before surgery. In all 4 patients, the findings observed by transesophageal echocardiography were confirmed at surgery. Finally, in 4 patients with nondiagnostic transthoracic studies, the transesophageal echocardiogram showed no abnormality. One of these patients had a clinical picture of sepsis, but without involvement of the porcine aortic prosthesis, which showed only minimal fibrosis and mild aortic regurgitation. In addition, 2 of these 8 patients also had mitral valve prostheses.

Transesophageal echocardiography was inadequate in 2 patients (6%), with the transthoracic approach better visualizing the aortic valve replacement. Both patients had concomitant mitral valve prostheses. Transthoracic studies revealed normal functioning aortic prostheses in these 2 patients.

The study of valve morphology and function has significantly improved with the use of transesophageal echocardiography.[6] Several studies showed that transesophageal echocardiography is very accurate for studying mitral valve abnormalities in either native or prosthetic valves and for diagnosing infective endocarditis.[1,2] The proximity of the transducer to the heart, without interference from the thoracic wall or lung tissue, produces higher quality images. This is very important in artificial valves, where the presence of synthetic material causes shadowing of heart structures, and particularly in patients with mitral valve prostheses, in whom the left atrial side of the prostheses can be visualized free of any valve artifacts. Furthermore, the use of color Doppler flow makes it possible to analyze trans- and periprosthetic regurgitations. It also allows use of higher frequency transducers, which results in higher resolution and consequently higher diagnostic accuracy than is regularly achieved with the transthoracic approach.

The advantage of transesophageal over precordial echocardiography in the study of the aortic valve is not as clear as in that of the mitral valve. Anecdotal case reports[4,5] and small series of patients[6] show some evidence favoring the use of transesophageal echocardiography in the assessment of aortic valve disease. However, this has not been consistently shown, and previous work from our laboratory showed the difficulty in visualizing the leaflets of aortic tissue prosthetic valves.[1] In the present study we compared transesophageal and precordial echocardiography in patients with bioprosthetic aortic valves and related it to the clinical and surgical data available.

In our study, 8 patients (24%) had transesophageal studies superior to precordial ones. Transesophageal echocardiography was particularly important in the diagnosis of aortic annular abscesses, torn leaflets and fistula between the left ventricle and right atrium. This agrees with previously published case reports in which transesophageal echocardiography detected sinus of Valsalva aneurysms associated with infected native and prosthetic valves, which were subsequently confirmed at surgery.[4,5] This study also shows that transesophageal echocardiography is particularly useful to visualize the posterior aspects of the aortic valve and annulus, which are closer to the esophagus. Daniel et al[7] recently reported on the value of transesophageal echocardiography in the detection of abscesses associated with endocarditis. They studied 118 patients and obtained a sensitivity and specificity for the detection of abscesses associated with endocarditis of 28.3 and 98.6%, respectively, for transthoracic echocardiography, and 87.0 and 94.6%, respectively, for transesophageal echocardiography. The same study also showed that abscesses were more frequent in aortic than

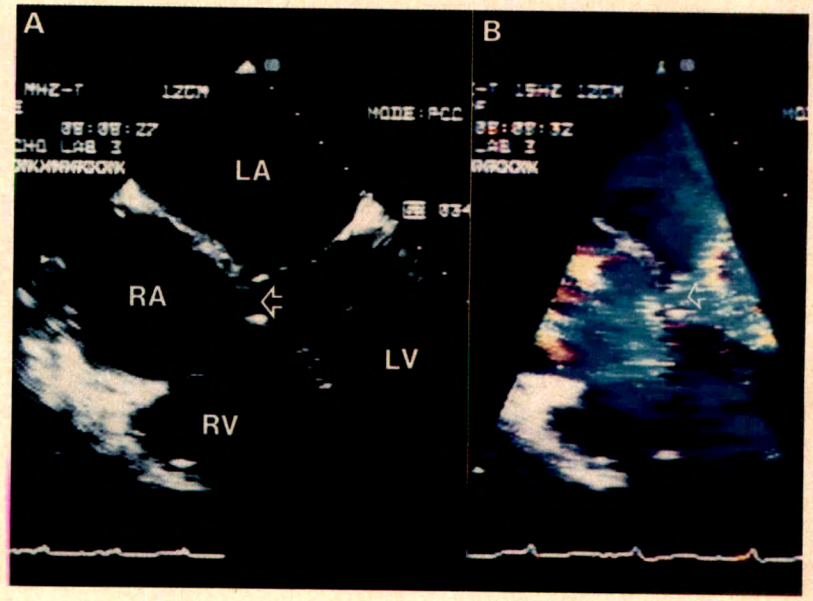


FIGURE 2. Fifty-four-year-old patient with bioprosthetic aortic valve and clinical diagnosis of infectious endocarditis. *A*, transesophageal echocardiogram shows left ventricular to right atrial fistula *(open arrow)* confirmed by color Doppler flow *(B)*. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

in mitral valve endocarditis. In 2 of our patients, transesophageal echocardiography was unable to properly visualize the aortic valve. In all of these patients, a mitral prosthesis was present. Therefore, an important limitation in visualizing the aortic valve with transesophageal echocardiography is the presence of a concomitant prosthetic mitral valve. One must conclude that transesophageal and transthoracic echocardiography are complementary and not exclusive in the study of aortic valve disease. The recent introduction of biplane probes with the ability to obtain 2 perpendicular scan planes may increase the diagnostic yield of transesophageal echocardiography in the study of the aortic valve. Further studies are necessary using this approach.

In the setting of infective endocarditis, Taams et al[2] recently showed that transesophageal echocardiography is superior to the precordial approach. In their study, precordial echocardiography did not show vegetations in any of 12 patients with prosthetic valve endocarditis (including 10 patients with prosthetic valves in the aortic position), whereas transesophageal echocardiography showed vegetation in 4. They concluded that transesophageal echocardiography is the best diagnostic approach when infective endocarditis is suspected in patients with either native or prosthetic valves.

The present study is a retrospective analysis; therefore, some minor clinical information may have been overlooked in some patients. In addition, surgery was performed in only 13 patients, although relevant clinical follow-up was accomplished in all. Transthoracic studies were performed before transesophageal ones; thus, the patient cohort is necessarily biased, because patients were selected based on the transthoracic results. However, in routine clinical practice, transthoracic studies always precede transesophageal echocardiography and should be seen as complementary. The use of single-plane probes is also a limitation. Further studies using bi- or omniplane probes may enhance our ability to diagnose aortic valve abnormalities, particularly in patients with concomitant mitral valve prosthesis.

The present study shows that transesophageal echocardiography is an important complementary technique in the study of aortic valve disease with some advantages over precordial echocardiography. It is particularly useful in the visualization of the posterior aspect of the aortic valve, annulus and root, and should be performed any time a periannular abscess or perivalvular leak is suspected. In addition, some patients were managed based on transesophageal findings only, without being subject to the extra risk and cost of cardiac catheterization. However, the present study also shows some limitations of transesophageal echocardiography, especially the presence of concomitant mitral prostheses, owing to the shadowing of the left ventricular outflow tract and the valve itself. Transesophageal echocardiography is indicated when transthoracic echocardiography does not provide adequate information; both should be considered complementary techniques in the evaluation of aortic valve disease.

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Localization of Mitral Periprosthetic Leaks by Transesophageal Echocardiography

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Optimal visualization of mitral regurgitant jets, and the absence of acoustic shadowing in the left atrium from prosthetic material account for the increasing use of transesophageal echocardiography (TEE) in evaluating mitral prostheses in the outpatient clinic,[1–3] as well as in the operative room.[3–5] This study was undertaken to evaluate the accuracy of TEE in predicting the surgical location of mitral periprosthetic leakage.

From November 1988 to December 1990, 6 patients (3 men and 3 women, aged 46 to 67 years, mean age 56) were studied with TEE for mitral valve prosthesis dehiscence (Carpentier-Edwards, n = 2; Bjork-Shiley, n = 2; Starr-Edwards, n = 1; Medtronic-Hall, n = 1) (Table I). Five of these patients were referred to our institution for newly developed mitral regurgitant murmurs, as well as for signs and symptoms of congestive heart failure. At the time of the study, the prosthetic valves were in place from 4 months to 14 years (mean 85 months). TEE was

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performed on awake patients to confirm a previous diagnosis obtained by transthoracic echocardiography (2 cases), or because of technically inadequate transthoracic imaging (3). In 1 of the 5 patients (no. 5), endocarditic vegetation was demonstrated at the valve sewing ring by 2-dimensional TEE, but not by 2-dimensional transthoracic echocardiography. Cardiac catheterization was performed in all patients but 1 and confirmed the diagnosis of periprosthetic leak.

In the remaining patient (no. 6), the periprosthetic leak was discovered by routine intraoperative TEE immediately after mitral valve replacement with a Med-

TABLE I Location of Mitral Prosthetic Dehiscence by Transesophageal Echocardiography and During Surgery in Six Patients

Pt.	Age (yr) & Sex	NYHA Class	Prosthesis (type)	Dehiscence Location: TEE–2D (quadrant)	Dehiscence Location: TEE–CFI (quadrant)	Surgery	Operative Procedure
1	57F	III	Carpentier-Edwards	Posterior	Medial, posterior	2–5 o'clock	Valve rereplacement
2	64M	IV	Starr-Edwards	—	Lateral	6–9 o'clock	Leak closure
3	49M	IV	Bjork-Shiley	Anterior, medial	Anterior, medial	9–1 o'clock	Valve rereplacement
4	60F	III	Bjork-Shiley	Medial, posterior	Medial, posterior	2–5 o'clock	Leak closure
5	60F	IV	Carpentier-Edwards	Posterior	Posterior	3–5 o'clock	Valve rereplacement
6	53M	III	Medtronic-Hall	—	Lateral	7 o'clock	Leak closure

CFI = Doppler color flow imaging; NYHA = New York Heart Association; TEE = transesophageal echocardiography; 2D = 2-dimensional.

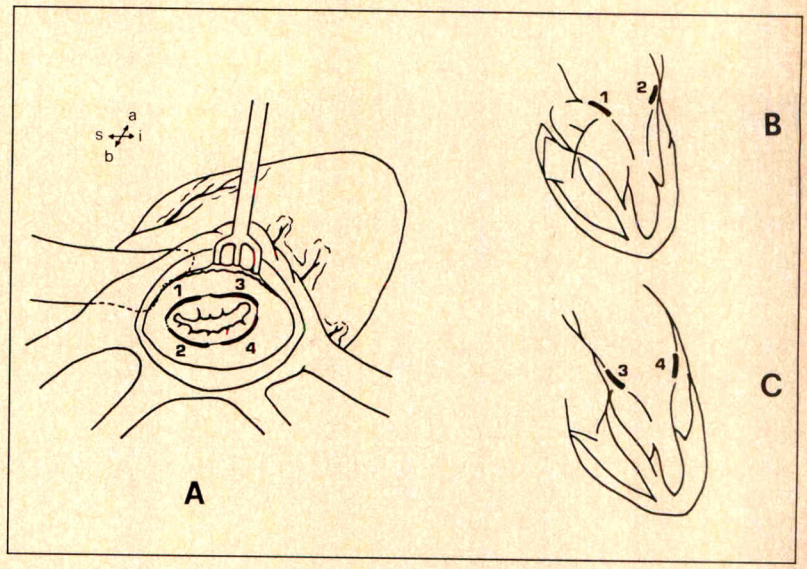


FIGURE 1. *A*, schematic drawing showing surgical view of mitral annulus. Left atrium is opened through incision parallel to interatrial groove. a = anterior; b = basal; i = inferior; s = superior; 1 = anterior quadrant; 2 = lateral quadrant; 3 = medial quadrant; 4 = posterior quadrant. *B*, schematic drawing of transesophageal 5-chamber view. *C*, schematic drawing of transesophageal 4-chamber view.

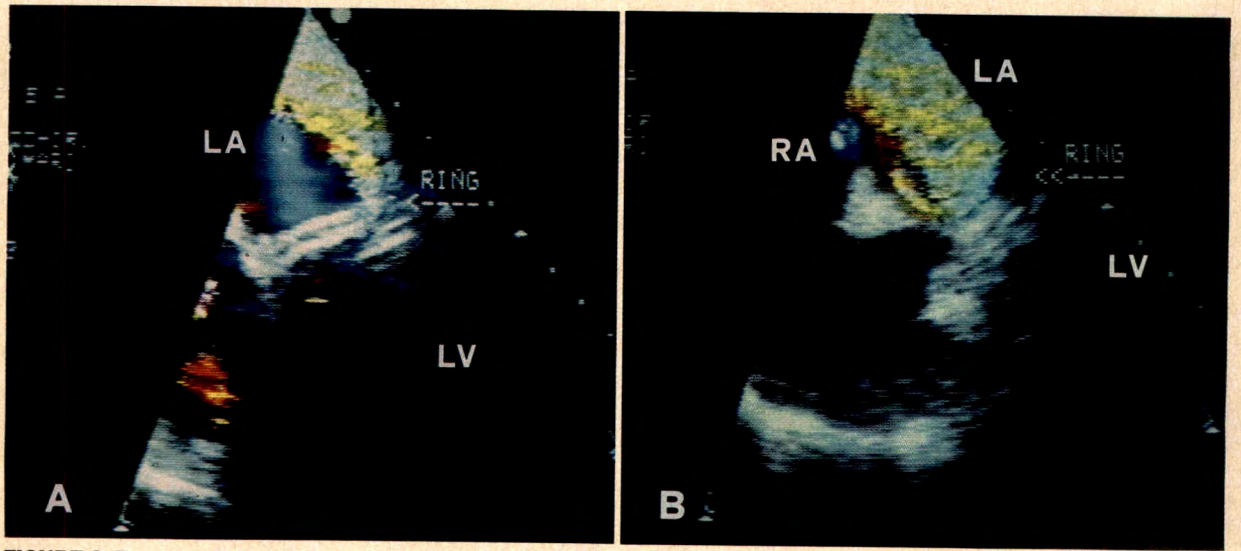
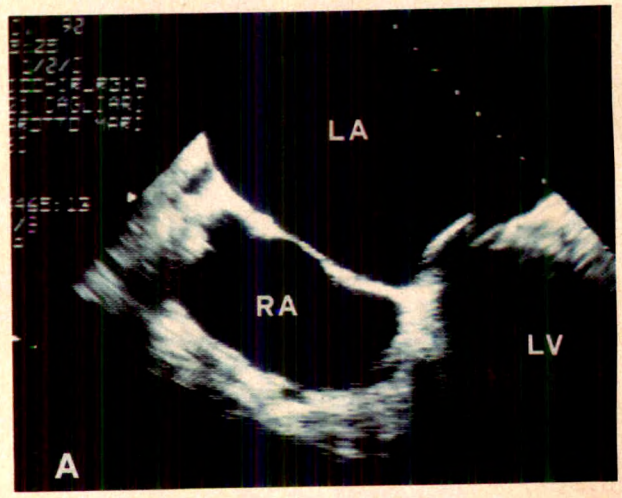


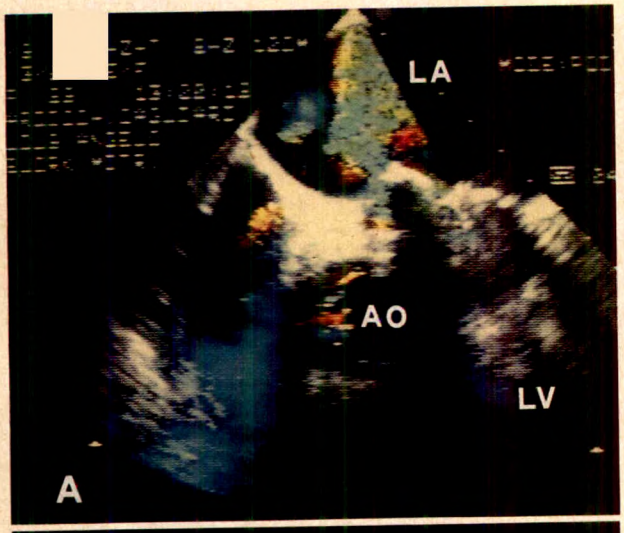
FIGURE 2. Transesophageal Doppler color flow imaging in patient with periprosthetic leak of Carpentier-Edwards mitral valve (case 1). Turbulent regurgitant jet is seen arising outside posterior *(A)* and medial *(B)* quadrants of prosthetic ring. LA = left atrium; LV = left ventricle; RA = right atrium.

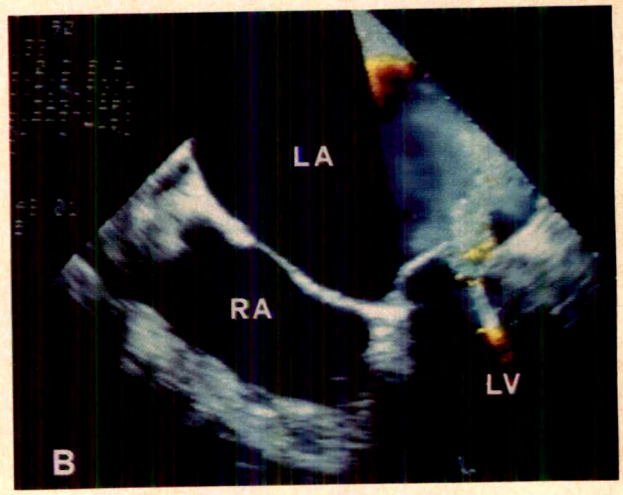
tronic-Hall prosthesis. This was the only case in which a periprosthetic leak was detected by intraoperative TEE in a series of 38 consecutive patients who had undergone surgery for mitral valve replacement. The prosthetic valve was replaced in 3 patients and resutured in the other 3.

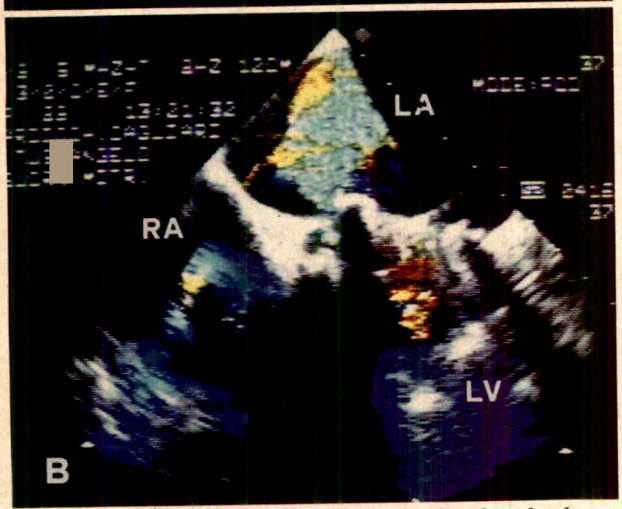
TEE with Doppler color flow imaging was performed with a Hewlett-Packard ultrasound system (Sonos 500 or 1000) using a 5 MHz phased-array transducer (model 21362A). All TEE studies were well-tolerated, and no complications were observed.

Visualization of the prosthetic mitral valves and regurgitant flow was obtained in the 4- and 5-chamber views with the transducer positioned behind the left atrium. Regurgitant jets were considered to be periprosthetic when they originated outside the valvular sewing ring. To clearly define the origin and the spatial extension of the periprosthetic jets, the echocardiographic mitral annulus was divided in 4 conventional quadrants similar to those used in surgery (i.e., anterior, 9 to 12 o'clock; medial, 12 to 3; posterior, 3 to 6; lateral, 6 to 9) (Figure 1). Beginning at the 4-chamber view, each quadrant was carefully scanned by manipulating the probe up and down behind the left atrium. The location of the leak was considered medial or posterior, or both, when periprosthetic jets flowed along the interatrial septum or the









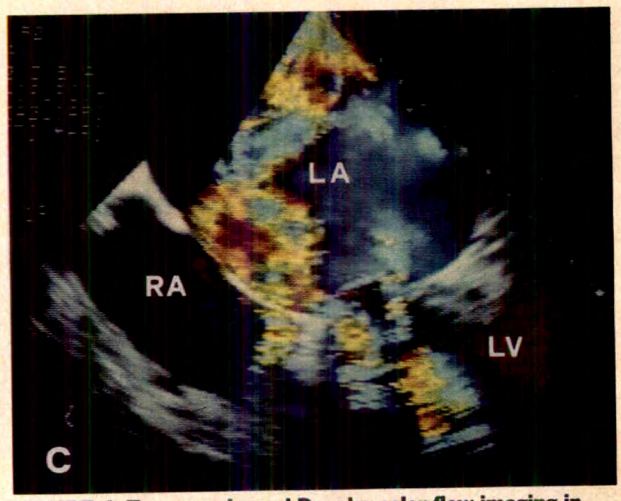


FIGURE 3. Transesophageal Doppler color flow imaging in patient with periprosthetic leak of Bjork-Shiley mitral valve (case 3). Turbulent regurgitant jet is seen originating outside anterior (A) and medial (B) quadrants of prosthetic ring. With systole, the valve moves up in left atrium, and clear detachment is visible. AO = aorta; other abbreviations as in Figure 2.

FIGURE 4. Transesophageal Doppler color flow imaging in patient with periprosthetic leak of Bjork-Shiley mitral valve (case 4). Clear detachment of posterior and medial quadrants of prosthetic ring is seen (A). Turbulent regurgitant jet is seen arising outside posterior (B) and medial (C) quadrants of prosthetic ring. Abbreviations as in Figure 2.

free wall of the left atrium, or both, respectively, in the 4-chamber view. The location of the leak was considered anterior or lateral, or both, when periprosthetic jets flowed along the aortic root or free wall of the left atrium, or both, respectively, in the 5-chamber view.

Table I lists the clinical characteristics of the patients, and the location of the mitral prosthetic dehiscence identified by TEE and during surgery. Representative echocardiograms are shown in Figures 2 through 5.

Compared with the transthoracic approach, TEE offers important advantages in evaluating patients with mitral valve prostheses.[1] Because the probe is positioned behind the posterior wall of the left atrium, reverberations from the mitral prosthesis are projected into the left ventricle and do not mask the color flow imaging of the left atrium. In addition, the close proximity of the esophageal transducer to the left atrium, and the parallel orientation of the ultrasound beam to the flow moving away from the mitral valve provide high quality imaging of the atrial side of the prosthesis, as well as of the regurgitant flow into the left atrium.

In this study, all the mitral periprosthetic jets exhibited multicolored mosaic patterns corresponding to high velocity and turbulent flows, filling large areas of the left atrium. In addition, TEE with Doppler color flow imaging was more sensitive than 2-dimensional TEE alone in detecting periprosthetic leaks. In fact, periprosthetic jets were present without any visible gap related to valve dehiscence in 2 patients.

The mitral annulus was conventionally subdivided in 4 quadrants to establish common reference points for the cardiologist and the surgeon. Although the landmarks used by the cardiologist in defining each quadrant differ slightly from those used by the surgeon, there was always a strict correspondence between the quadrants indicated by TEE and those visualized by the surgeon. Our findings demonstrate that in all 6 patients localization of the mitral periprosthetic jets correlated precisely with the findings at surgery. Therefore, the search for a dehiscence with a probe is unnecessary and, furthermore, potentially dangerous in a weak annulus. With the information obtained by TEE, the surgeon can now direct his attention to a well-defined portion of the suture line.

Acknowledgment: We thank Achi Ludomirsky, MD, for helpful comments, and Jan S. Radakovich, MS, Ed, for assistance in editing the manuscript.

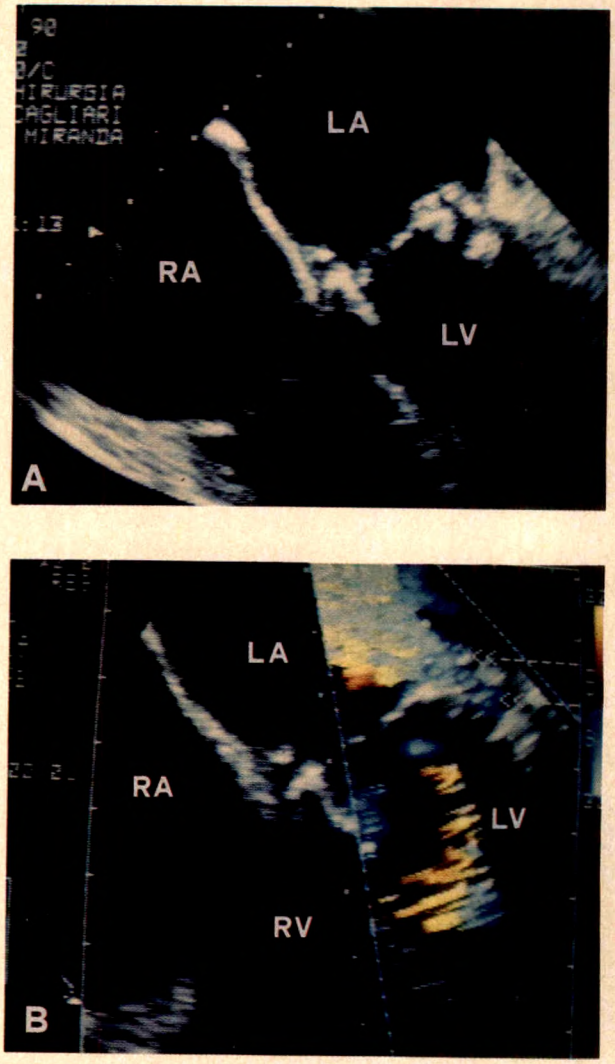


FIGURE 5. Transesophageal Doppler color flow imaging in patient with periprosthetic leak of Carpentier-Edwards mitral valve (case 5). Echodense vegetative material is seen attached to posterior side of both prosthetic ring and natural valve annulus. Clear prosthetic dehiscence is noted *(A)*. Turbulent regurgitant jet arising outside posterior quadrant of prosthetic ring is clearly demonstrated *(B)*. RV = right ventricle; other abbreviations as in Figure 2.

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Transesophageal Echocardiographic Detection of Atrial Septal Defect in Adults

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Many studies have described the detection and quantitation of atrial septal defect (ASD) by 2-dimensional and Doppler color flow echocardiography.[1–12] Subxyphoid 2-dimensional echocardiography provides excellent imaging of the interatrial septum in infants and children, but this approach often does not visualize ASD in adults.[11] Recently, transesophageal echocardiography (TEE) has provided a new acoustic window to the heart and high-quality imaging of the interatrial septum is easily obtained.[13–18] This study assesses the sensitivity, specificity and accuracy of TEE and transthoracic echocardiography (TTE) in the diagnosis of ASD in adult patients.

One hundred and twenty-two consecutive patients who underwent TTE and TEE were enrolled in this study. Patients were divided into 2 groups: group 1 consisted of 80 patients (34 men and 46 men, aged 17 to 77 years [mean 46 ± 17]) who had various diseases; group 2 consisted of 42 patients (10 men and 32 women, aged 28 to 70 years [mean 48 ± 13]) with mitral stenosis who were candidates for balloon mitral valvuloplasty. Group 2 was used as a control group. Cardiac catheterization was performed in all 122 patients and surgery was performed in 66 of them. Among the 80 patients in group 1, 1 patient had both an ostium primum and secundum ASD, 38 patients had an ASD, and 41 patients had no ASD.

TTE was performed using either an Advanced Technology Laboratory Ultramark 6 system or a Hewlett-Packard 77020A Ultrasound imaging system with a 2.5 or 3.5 MHz transducer. The parasternal long-axis, short-axis, apical 4- and 2-chamber views, subcostal, and modified apical long- and short-axis planes were studied. The ASD was categorized as sinus venosus, ostium secundum or ostium primum defect according to whether the defect location was in the superior, middle or lower portion of the atrial septum. The echocardiographic data were studied by an observer unaware of the catheterization findings.

TEE was performed with a 5 MHz phased-array transducer attached to the tip of a modified endoscope. The scope was connected to a Hewlett-Packard cardiac ultrasound system (77020A). Each patient was premedicated with 10% lidocaine spray to the posterior pharynx and sedated with diazepam. Food intake was withheld for at ≥4 hours before procedure. The ASD was categorized as sinus venosus, ostium secundum or ostium primum defect depending on the defect location (Figure 1).

Cardiac catheterizations with full oximetric and left and right heart hemodynamic studies were performed on all 122 patients. A step-up in oxygen saturation at the right atrium by >7% indicated the presence of an ASD.[19] Multiple oximetry samplings (3 to 5 samples) in the

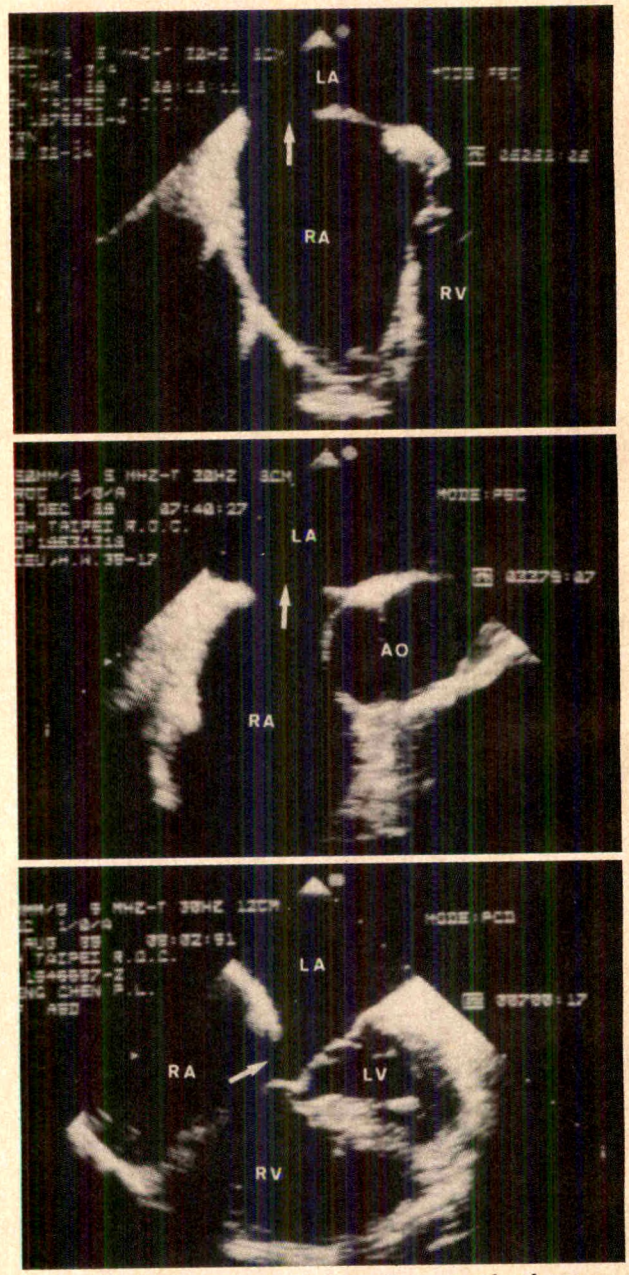


FIGURE 1. Transesophageal echocardiograms of a sinus venosus *(upper)*, ostium secundum *(middle)* and ostium primum defect *(lower)*. AO = aorta; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

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right atrium were obtained with meticulous care in all patients. Surgery was performed in 66 patients: 25 with and 41 without ASDs. The 25 patients with ASD had 26 defects including 19 with a secundum, 3 with a primum, 2 with a sinus venosus and 1 patient with both a secundum and primum ASD.

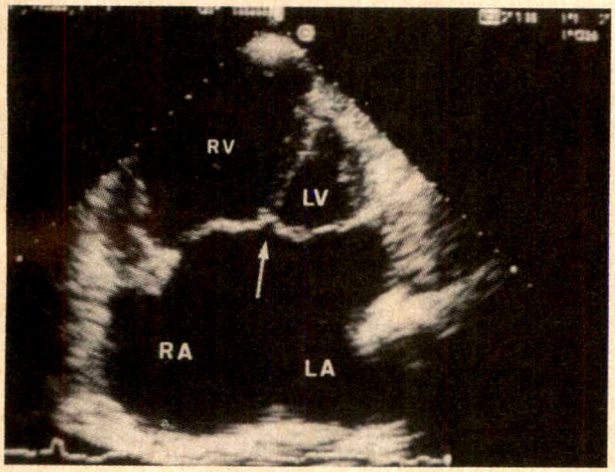
Transthoracic 2-dimensional echocardiography identified 33 of 39 patients with an ASD (sensitivity 85%). The addition of color flow imaging identified 2 more patients who were classified as doubtful ASD cases by 2-dimensional echocardiography alone. Color Doppler echocardiography increased the diagnostic sensitivity to 90%. There were no false-positive cases; the specificity was 100% in the diagnosis of ASD by TTE (Table I). Defects in 4 patients were not detected by TTE: 3 patients were technically difficult to study; the defect in another patient was missed because of a small secundum ASD. A patient with a large secundum ASD was falsely diagnosed as having both a primum and a secundum ASD by TTE because of the underestimation of the lower interatrial septum (Figure 2, top). TEE identified the residual lower septum clearly and he was demonstrated to have a large secundum ASD after operation (Figure 2, bottom). In addition, a primum ASD in 4 patients was clearly identified. TTE accurately classified ASD in 34 patients (4 missed, 1 overdiagnosed, accuracy = 94%).

TTE identified ASD at the superior atrial septum in 2 patients with a sinus venosus ASD, but did not visualize the associated anomalous pulmonary venous connection. Cardiac catheterization and operation found that the right upper pulmonary vein was connected to the superior vena cava in one and the right lower pulmonary vein was connected to the junction of both atria in the other patient.

TABLE I Comparison of Transthoracic and Transesophageal Echocardiography in the Diagnosis of Atrial Septal Defect

	TTE		TEE	
	ASD (+)	ASD (0)	ASD (+)	ASD (0)
ASD (+)	35	4	39	0
ASD (0)	0	41	0	41

ASD = atrial septal defect; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography; + = positive; 0 = negative.



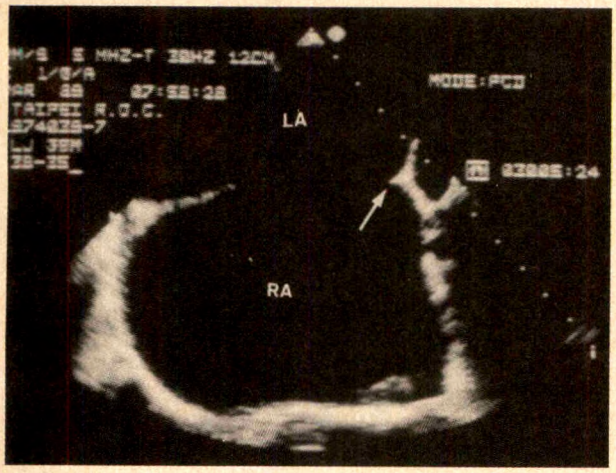


FIGURE 2. ***Top,*** **modified parasternal 4-chamber view of a patient with a large secundum atrial septal defect (ASD); the lower septum** ***(arrow)*** **was almost absent and he was falsely diagnosed as having both a secundum and a primum ASD on transthoracic echocardiography.** ***Bottom,*** **tiny septum** ***(arrow)*** **was visualized from transesophageal approach, indicating that this patient had a secundum ASD. Abbreviations as in Figure 1.**

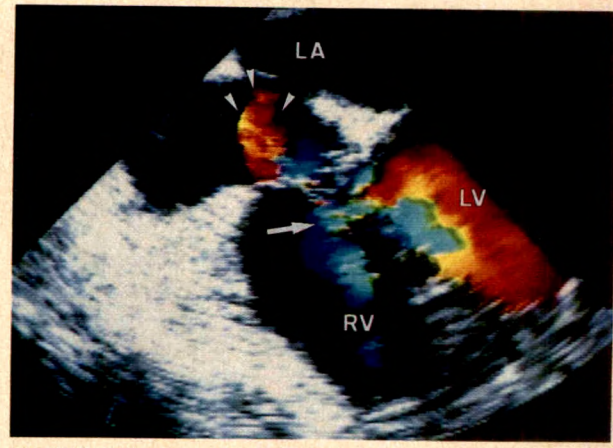


FIGURE 3. Transesophageal echocardiogram demonstrating ventricular septal shunted flow ***(arrow)*** **and tricupid regurgitation** ***(arrowheads)*** **occurring at the same time. Abbreviations as in Figure 1.**

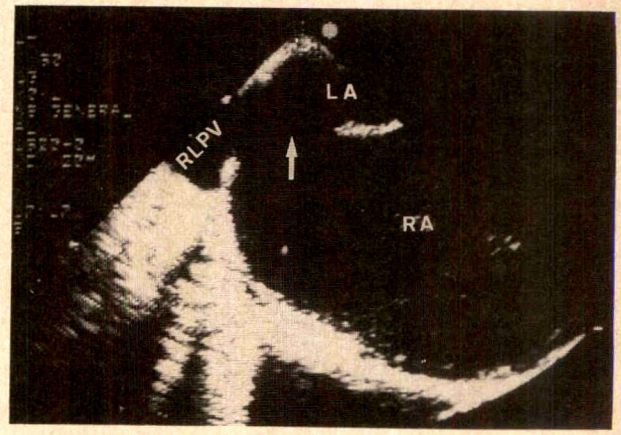


FIGURE 4. Transesophageal echocardiogram of a patient with a sinus venosus defect ***(arrow).*** **The right lower pulmonary vein (RLPV) draining into the junction between right and left atrium (RA, LA) is seen.**

TEE identified 38 of 39 patients with ASD (sensitivity 97%). One small defect (0.3 cm in size) was visualized with the assistance of color flow imaging. Two patients were initially suspected of having a ventricular septal defect and an ASD. TTE and TEE both identified the ventricular septal defect with left to right shunt flow, tricuspid regurgitation, right ventricular enlargement and paradoxical septal motion, but without transatrial septal shunt flow (Figure 3). Cardiac catheterization demonstrated that they had a step-up in oxygen saturation at both the atrial and ventricular levels as well as easy passage of the catheter from right to left atrium, suggesting the presence of a ventricular septal defect and an ASD. However, only a ventricular septal defect was found at the time of surgical interventions. With a combination of color flow and anatomic imaging, TEE had a sensitivity of 100%, specificity of 100% and accuracy of 100% in detecting and localizing the ASD (Table I). TEE clearly visualized the sinus venosus defects in 2 patients and an anomalous pulmonary vein draining into the junction of both atria in one (Figure 4), but not in another patient with connection to the superior vena cava.

Group 2 patients had rheumatic mitral stenosis and all underwent TTE, TEE and cardiac catheterization. Although echo dropout of the thin fossa ovalis membrane from the TTE approach was common, the addition of color flow imaging avoided the false diagnosis of ASD. Both TTE and TEE had a specificity of 100% in excluding the diagnosis of ASD in this control group.

TEE provided excellent visualization of the ASD noninvasively. The ability of color flow imaging to visualize the shunt flow across an ASD is further proof of the diagnosis. Although TTE, using 2-dimensional and Doppler color flow imaging, has allowed direct visualization of ASD with a sensitivity of 70 to 97%,[2,3,9–11] both false-positive and false-negative results due to suboptimally recorded images occur. Our study found that TTE had a sensitivity of 85% in identifying ASD and the addition of color flow imaging increased the diagnostic sensitivity to 90%. TTE accurately localized ASDs in 34 of 39 patients (accuracy 94%). TEE visualized all ASDs (sensitivity 100%, specificity 100%, and accuracy 100%) in these 39 patients. Based on our experience, we believe that cardiac catheterization may not be necessary in adult patients with ASD, particularly at the present time, when pulmonary artery pressure can be estimated accurately and noninvasively with Doppler echocardiography.

In conclusion, TEE is more sensitive, specific and accurate than TTE in detecting and localizing ASD. TEE may be particularly useful whenever the precordial approach fails to confirm the clinically suspected case of ASD.

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Location, Localization and Surgical Treatment of Cardiac Pheochromocytoma

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Pheochromocytoma is a rare tumor. It can occur at any site in the sympathoadrenal system. Most lesions occur within the adrenal gland; <2% occur within the chest and most of these are located in the posterior mediastinum.[1] Twenty intrapericardial lesions were reported (17 outside or on the surface of the heart, and only 3 intracardiac [intracavitary]).[1-6] Although intrapericardial pheochromocytomas are exceedingly rare they are being reported with increasing frequency, probably because of improved diagnostic techniques. Diagnosis and localization are important because surgical resection is often feasible and potentially curative, because most pheochromocytomas are benign. This article reports an intracardiac pheochromocytoma that was successfully resected, discusses diagnostic techniques and reviews previous publications regarding location, localization and surgical treatment of such lesions.

A 15-year-old girl was referred in 1981 with history of sweating attacks. Her blood pressure was 150/110 mm Hg, and her urinary excretion of noradrenaline was 10,700 nmol/24 hours (normal 120 to 500) and of adrenaline 1,210 nmol/24 hours (normal 30 to 120). A computerized tomography scan showed the adrenal glands to be normal, but revealed a mass in the left atrium. After preoperative treatment with phenoxybenzamine and labetalol, a right thoracotomy was performed, but excision of the tumor was not considered feasible at that time. Subsequently an iodine-131 meta-iodobenzylguanidine scan was performed that outlined the tumor and confirmed it to be a pheochromocytoma. No evidence of metastases was found. The patient remained symptom-free on phenoxybenzamine and propranolol for 8 years during which her blood pressure was satisfactorily controlled, and she was able to fully participate in the activities of her teenage friends. Her growth and development were normal. She married in 1988, and an unplanned pregnancy occurred in 1989. Termination of pregnancy was advised because of the potential risk and was performed at 10 weeks gestation. The patient was referred to Harefield hospital. A repeat computerized tomography scan and iodine-131 meta-iodobenzylguanidine scintigraphy (Figure 1) showed no evidence of metastases. During surgery, the left atrium was markedly enlarged. The tumor located within the left atrial cavity was firmly attached to the wall of the atrium, had a lobulated surface and measured 15 × 9 cm. The tumor was supplied by numerous arteries arising from the posterior mediastinum (probably from the bronchial circulation) passing through the wall of the left atrium to reach the point of attachment. The tumor was resected while the patient underwent cardiopulmonary bypass, and the wall of the left atrium was reconstructed using a large patch of autologous pericardium. Histopathologic examina-

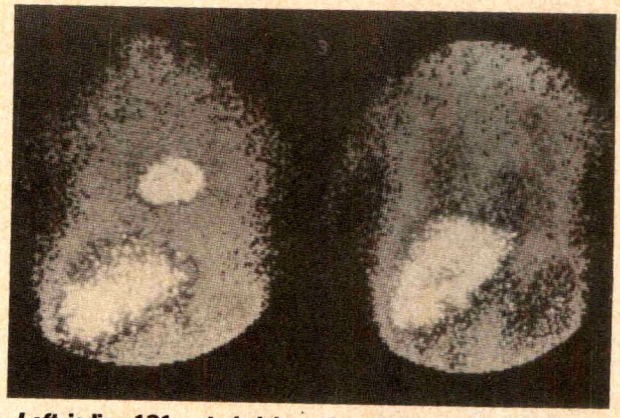


FIGURE 1. ***Left,*** **iodine-131 meta-iodobenzylguanidine scan of chest and upper abdomen (anterior view) demonstrating uptake in liver and within tumor situated in left atrium. There are no other areas of uptake suggestive of metastases.** ***Right,*** **repeat scan after resection of tumor.**

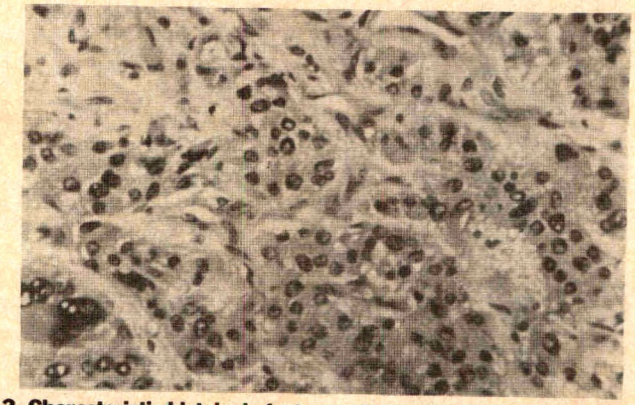


FIGURE 2. Characteristic histologic features of pheochromocytoma. Cells have abundant granular cytoplasm and rather uniform nuclei. Low-power examination (not shown) demonstrated that these cells were arranged in nests separated by relatively well-vascularized stroma. (Hematoxylin-eosin ×250, reduced by 50%.)

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TABLE I Data on 20 Previously Reported Cases of Cardiac Pheochromocytoma Together with the Present Case

No.	Year	Location	Size	Presentation	Localization	CPB	Surgical Approach	Outcome
1	1960[1]	AP window	—	—	—	—	—	—
2	1961[3]	LA surface	—	—	—	—	—	Died
3	1963[1]	Aortic root	—	Palpitation, murmur	Angiography	—	—	—
4	1974[5]	LA cavity	8 × 5	Palpitation, murmur	Angiography	Yes	Sternotomy	Alive
5	1978[3]	IA groove	8 × 9	Angina	Angiography	No	Sternotomy	Alive
6	1979[4]	RA cavity	—	SH	—	No	Right thoracotomy	—
7	1981[2]	AP window	—	—	I-MIBG, CT	Yes	Thoracotomy	Alive
8	1982[2]	LA surface	3 × 4 × 6	Palpitation, murmur	I-MIBG, CT	No	Sternotomy	Alive
9	1982[2]	LA surface	—	—	I-MIBG, CT	No	Thoracotomy	Alive
10	1982[2]	LA surface	—	—	I-MIBG, CT	No	Thoracotomy	Alive
11	1982[2]	IA groove	—	—	I-MIBG, CT	Yes	Thoracotomy	Died
12	1982[2]	LA surface	—	—	I-MIBG, CT	Yes	Thoracotomy	Alive
13	1982[2]	AV groove	4 × 5 × 6	Palpitation, angina, SH	Angiography	Yes	Thoracotomy	Alive
14	1982[1]	LA surface	5 × 5 × 3	SH	I-MIBG, CT	Yes	Sternotomy	Alive
15	1982[2]	LA surface	—	—	—	—	—	Alive
16	1982[1]	LA surface	5 × 3 × 3	SH	CT	—	—	Alive
17	1982[1]	IA groove	5 × 6	SH	I-MIBG, CT	Yes	Right thoracotomy	Alive
18	1983[1]	LA surface	6 × 12	SH	I-MIBG, CT	Yes	Right thoracotomy	Died
19	1985[6]	LA surface	—	—	—	Yes	Sternotomy	Died
20	1989[4]	RA cavity	—	SH	I-MIBG	Yes	Sternotomy	Alive
21	1990	LA cavity	9 × 15	SH	I-MIBG	Yes	Sternotomy	Alive

AP = aorticopulmonary; AV = atrioventricular; CPB = cardiopulmonary bypass; CT = computerized tomography; IA = interatrial; I-MIBG = iodine-131 meta-iodobenzylguanidine; LA = left atrial; RA = right atrial; SH = systemic hypertension.

tion revealed the tumor to be a benign pheochromocytoma (Figure 2). The patient had an uneventful recovery after surgery, and imaging 2 weeks postoperatively showed no evidence of residual tumor (Figure 1). Uptake of iodine-131 meta-iodobenzylguanidine by the myocardium was absent before surgery, but showed a normal pattern after the tumor was excised. The patient's blood pressure returned to normal levels without medication, and urinary catecholamine levels returned to the normal range.

Because pheochromocytomas are usually benign, surgical resection may be curative. Although medical therapy can control hypertension, it may not protect the patient from a hypertensive crisis during stress. The details of the 20 previously reported cases of cardiac pheochromocytomas that were treated surgically are listed in Table I. The location of each tumor is shown in Figure 3. Successful resection of these lesions depends on diagnosis and localization before surgery. Improvements in cardiac imaging techniques have contributed to the management of such cases. The iodine-131 meta-iodobenzylguanidine scan is particularly helpful in localizing and confirming the nature of a pheochromocytoma, but it does not provide precise information about the local extent and anatomical relations of the lesion. It can also provide preoperative information on the presence and extent of unanticipated metastases.[1-2] Two-dimensional echocardiography is noncontributory in most cases, because the extent of the tumor cannot be clearly defined.[2] Theoretically, transesophageal echocardiography may be of value, although its use has not been reported in cardiac pheochromocytoma. Coronary angiography may reveal the tumor circulation, which should be taken into consideration during surgery.[2] If necessary, the precise spatial relations of the tumor to adjacent cardiac structures can be dem-

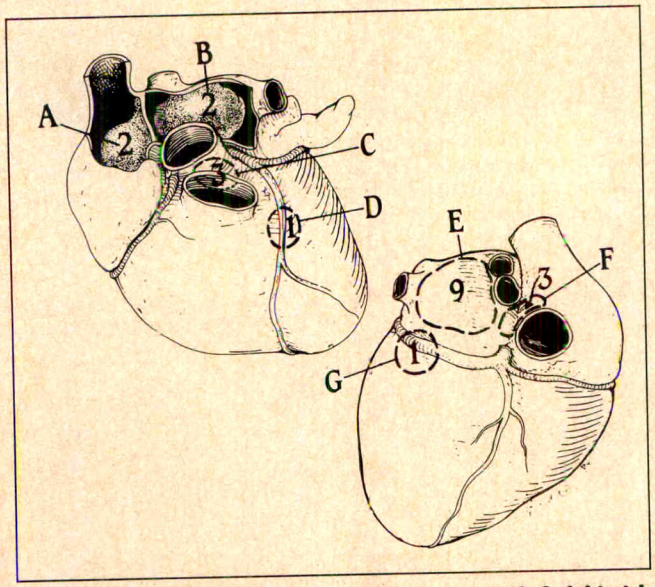


FIGURE 3. Distribution of 21 cardiac pheochromocytomas. *A*, 2 right atrial intracavitary tumors arising from interatrial septum. *B*, 2 left atrial intracavitary tumors (1 arising from posterior wall, and present case that arose from roof of left atrium). *C*, 3 tumors located at root of great arteries. *D*, 1 tumor on left ventricular surface involving left anterior descending coronary artery. *E*, 9 tumors on outer surface of left atrial wall. *F*, 3 tumors in interatrial groove. *G*, 1 tumor in atrioventricular groove.

onstrated by magnetic resonance imaging, because of its high contrast resolution and multiplane imaging capacity.[4] In the present case, dynamic computerized tomography scanning localized the tumor to the left atrium, and scintigraphic scanning confirmed its nature and excluded metastases. The location of the tumor indicated that the major coronary arteries were not involved. In this case, cardiopulmonary bypass was performed before handling the left atrium to reduce the risk of intraoperative hypertension. Cardiac pheochromocytomas do not "shell out" from adjacent tissues, as in the case of tumors in the abdomen or posterior mediastinum.[1] In this case, the tumor was located within the cavity of the left atrium with extensive infiltration of the wall. Complete removal of the tumor could only be achieved by a full thickness excision of the atrial wall and by replacement with a pericardial patch. In another case where the lesion was intimately related to the coronary arteries, the tumor could only be excised by reimplanting the left main coronary artery and performing a bypass graft to the circumflex coronary artery.[1] The highly vascular nature of these tumors was demonstrated in 3 patients who died of intraoperative hemorrhage.[4] Large nutrient tumor vessels must be identified and tied before dissection. If the lesion is not resectable using conventional techniques, explantation of the heart, and "bench" surgery followed by autotransplantation has been used.[6] Provided that the tumor is confined to the heart, allotransplantation may be a therapeutic option, as it is in other types of cardiac tumors.[7]

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Decreased Heart Rate Variability in Congestive Heart Failure

In the May 15, 1991 issue, Casolo et al,[1] using power spectral analysis techniques, reported that "heart rate variability is greatly reduced in patients with congestive heart failure." However, their study group consisted of 15 patients with decreased left ventricular function secondary to coronary artery disease (CAD). The investigators mistakenly stated that the study by Kleiger et al[2] demonstrated that "heart rate variability is a powerful independent prognostic factor in patients with CAD." Kleiger, however, studied heart rate variability only in patients with CAD who had sustained myocardial infarction. The independent association between heart rate variability and CAD is unknown. Other investigators have attempted to understand this relation, but the results are conflicting. Hayano et al,[3,4] using the "coefficient of component variance," have shown in 2 reports that decreased vagal tone is correlated with the extent and severity of CAD. Rich et al,[5] defining heart rate variability as the "standard deviation of 5-minute means of sinus cycle lengths," did not find this to be the case. Therefore, it would be of great interest to know the degree of CAD in Casolo's subjects.

It is well known that myocardial ischemia and infarction influence neural activity in the heart independent of their effect on left ventricular function.[6] Thus, Casolo's study group had 2 potential reasons for alteration of the sympathovagal balance. It is not clear from the presented data whether the pathologic process of congestive heart failure or CAD exerted a greater effect on autonomic tone. Furthermore, the absence of a standard definition of heart rate variability only serves to further cloud this issue.

James E. Carter, Jr., MD
Chicago, Illinois
29 May 1991

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REPLY: The comments made by Carter raise several interesting points of discussion. Although it is not clear whether the presence and extent of coronary artery disease (CAD) affect heart rate (HR) variability, it is generally accepted that HR variability is decreased in congestive heart failure (CHF).[1,2] Although designed for different purposes, other studies using HR spectral analysis showed that the total power of HR variability spectra (a measure of HR variability) is greatly reduced in patients with CHF compared with normal subjects.[3,4] Also, in Kleiger et al's[5] study, HR variability was inversely and significantly correlated with all available measures of pump failure. Thus, HR variability is decreased in patients with CHF and it is also associated with decreased left ventricular function.

With regard to Carter's question, in our more recent study,[4] all patients had multivessel CAD. In particular, 12 patients had 3-vessel and the remaining three 2-vessel disease.

Conflicting data[6,7] regarding the relation between HR variability and degree of CAD may depend on several factors. Differences in methodology and selection of patients may account for the results of the cited studies. For example, Rich et al[6] used the standard deviation of 5 minute means of sinus cycle lengths in milliseconds, and the mean left ventricular ejection fraction of their study group was 65 ± 14%. Hayano et al[7] used the high-frequency component of spectral composition of HR variability as a measure of "pure" vagal activity, and the mean left ventricular ejection fraction of their patients was significantly decreased with the advancing severity of CAD. In fact, it cannot be excluded that the apparently conflicting results of these 2 investigations may be explained specifically by a difference in the left ventricular function of the patients studied.

Neural activity of the heart can be influenced by several different factors including acute myocardial ischemia and infarction, left ventricular dysfunction, diabetic autonomic neuropathy, and so forth. With regard to the specific point raised by Carter, although it is theoretically possible that ischemia and infarction may play a major role in the impaired neural activity of the heart observed during CHF, it is, however, difficult to differentiate the effect of CHF, per se, from that of a primary neural impairment (for example, purely "ischemic"). Frequently, CHF secondary to CAD is the result of 1 or more previous infarcts, and there are no studies comparing HR variability in CHF secondary to CAD with that in CAD without CHF. In a previous study[1] we did not find any difference in HR variability be-

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tween patients with CHF secondary to CAD and those with CHF secondary to primary cardiomyopathy. Therefore, the observed reduction in HR variability seems related to CHF rather than to its etiology.

The apparent confusion due to the absence of a standardized definition of HR variability in some cases reflects the aim to obtain different information from the same biological phenomenon. Until the physiology and physiopathology of HR variability is clearly established, a common nomenclature and standardization of methods is probably not possible and, in any case, difficult to achieve.

Finally, Carter states that I mistakenly cited Kleiger et al's[5] study conclusions. As a matter of fact, Kleiger studied patients who had had a prior myocardial infarction (MI). However, (1) patients with MI usually also have CAD, and, as Carter noted, the independent weight of either previous MI or CAD to HR variability is not yet clear, (2) the context in which the reference is cited is not relevantly affected by the specification that patients with CAD also had MI, and (3) Rich et al's[6] study that explored the correlation between HR variability and late mortality after coronary angiography in patients with CAD does not provide substantially different results from Kleiger, as it confirms the value of decreased HR variability as a potent independent predictor of mortality in patients with CAD even when patients did not suffer from a prior infarction.

Giancarlo Casolo, MD, PhD
Florence, Italy
12 July 1991

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Comment on the Implantable Defibrillator Backlash

Fogoros' article (The implantable defibrillator backlash. *Am J Cardiol* 1991;67:1424–1427) discusses and rejects the concepts put forth in an editorial of mine published about 2 years ago. It provides an opportunity for a response in order to correct misinterpretation. There has been little doubt from the very first animal and patient studies that the implanted cardioverter-defibrillator (ICD) has the ability to terminate ventricular tachycardia and fibrillation. Each of us who implants such devices is involved in inducing and terminating such arrhythmias so frequently that the observation is now commonplace. Clinical practice has repeatedly demonstrated successful rescue from sudden cardiac death. The issue I raised was the ICD's overall impact on patient survival and longevity. The editorial[1] "ICD Benefit" referenced several of the earliest publications,[2,3] which reported the earliest ICD clinical evaluation. They contained important deficiencies including survival projections based on the receipt of a shock by fewer than half of the patients, without actuarial analysis, and comparison with published reports on control subjects without ICD therapy. Fogoros now states his agreement with my critique by writing that ". . . he (sic) defined 3 arguments that he rightly felt had not been adequately addressed in published reports: . . ." and later that ". . . the incidence of death, a longitudinal statistic, the value of which is meaningful only when calculated actuarially. Early reports failed to do this, and simply reported the proportion of ICD recipients who had received shocks at the time of data analysis." In the Furman editorial,[1] the incidence of shock at Montefiore Medical Center was 50%, higher than in any other article then published. It now seems clear that the earlier articles had a lower incidence of shock because patient follow-up (at the time of their publication) was briefer.

Fogoros then writes that in actuarial analysis his shock incidence is 64% at 4 years, another's is 67% (really 64%) at 16 months[4] and still another >50% at 20 months,[5] all mean follow-up periods. Finally he states that in a study of which I was the second author it was >80% at 4 years.[6] That figure was never given in that publication or elsewhere by our group, is incorrect and can be disregarded. As the published incidence of shock was <50% and no actuarial analysis had been performed, it took the publication of later manuscripts to demonstrate that, in an actuarial calculation, a higher shock incidence does occur. But what Fogoros did not write is that while the incidence of shock increases rapidly during the first year, its actuarial increase is not linear and there is no report in which the actuarial incidence of shock ever exceeds 80%. Indeed, it is now clear that the majority of ICD patients eventually do receive

a shock, but those who do not are healthier. Still they are usually calculated as having benefited by the implantation of the ICD, surely an issue that remains legitimately controversial.

Fogoros constructs argument 1, which is that implanters of the ICD ". . . need to select their patients more carefully." That was neither stated nor implied and I have made no implication that implanters are less than careful. The suggestion was made that despite workers' best efforts, some patients do not receive a shock and that a more valid determination of the true benefit of the intervention would be achieved by a different means of patient analysis. It may be unreasonable to expect complete diagnostic accuracy in so complex an issue as prediction of the recurrence of ventricular tachycardia or fibrillation, or both, but then, a statistical differentiation should be made between patients who receive an appropriate shock and those who do not. The issue of indications for implant is so important that professional organizations have now provided recommendations concerning patient selection.[7,8]

The second argument is that patients should be analyzed into 2 separate groups: those who have received a shock and those who have not. Undertaking the shock–no shock analysis, the 2 patient groups are quite different. The argument[5] that the 2 groups cannot be differentiated by any prospective analysis is not convincing because the groups are obviously different; some have received a shock, some have not. It may be that we cannot now distinguish them in advance, but that neither means that they can never be distinguished or that they are not different; perhaps they will be prospectively distinguished by a technique not now available.

The third argument, that benefit should be calculated from the first shock and not from implant, remains strong. The implanted ICD does not treat until it delivers a shock, though the more recent devices (still in clinical evaluation) can provide antitachycardia pacing, and for them, that alone can be definitive therapy. While some investigators have attempted to invoke a psychological benefit (and others have pointed out the need for emotional support for these patients) and even a benefit for the freedom to medicate differently, these are weak arguments. Indeed, it is now difficult to determine exactly whether a shock was appropriate, but technology and device-contained Holter monitoring is already helping with that issue and will surely help further. It is a common observation that we must know the cardiac rhythm before, during and after ICD therapy delivery.

The statement is made that ". . . there has never been a randomized controlled trial with the ICD. Such a study should have been conducted at the very beginning." We can hardly blame the inventors of the technique and device, when viewing this revolutionary success, that their first thoughts were not to undertake a randomized study. That was not their role and that time is past. However, a decade later we will not be excused so readily if we do not undertake the arduous but critical effort of careful data analysis. Some of that analysis depends on the perception from which the analysis is undertaken. Fogoros, himself, has made a critical contribution by pioneering the actuarial analysis of many longitudinal aspects of ICD therapy.[9]

The original editorial[1] was a plea to look more carefully at ICD data. That has been accomplished and is satisfying to its author. But we have not gone far enough. An actuarial analysis is only a mathematic technique. Until its users define their terms and the means of entering data and common definitions have been achieved, the data will remain controversial. For example, the earliest publications assumed that each shock was appropriate and that the alternative to a shock was sudden cardiac death. Patient longevity calculations were based on these assumptions; both are now widely rejected. But other changes of interpretation may be required. An almost simultaneous publication[10] raises these issues. There is no common agreement about how to calculate sudden cardiac death and operative mortality, which is between 1.5 and 6%. There is no agreement about how to calculate arrhythmic death and general cardiac (i.e., pump failure) death.[11] We have not agreed on how to deal with crossover therapy. Some believe that once an ICD is implanted, survival is always credited to it even if it is removed and not replaced, even if the crossover therapy is cardiac transplant[12] and the device has been definitively removed. Others believe that such patients should be censored at the time of crossover therapy, crediting the ICD with patient survival until it is removed, but not thereafter. Because the ICD is being considered as a bridge to transplant this definition will be quite important. Until these matters of definition have been resolved it is unlikely that we will be able to agree on the value of ICD therapy. Eleven years after the first ICD implantation and 6 years after the Food and Drug Administration release, these issues remain disputed and an organized effort at resolution should have been started long ago. It is probably unethical to conduct a randomized study of the general ICD implant population in the United States now, so we will have to await data from countries where the ICD has not yet achieved widespread therapeutic acceptance and in which our colleagues can conduct a randomized study. Funded studies of subsets of ICD patients are underway and these may resolve specific issues. As the numbers of ICDs continue to be implanted, and especially outside of institutions with thoughtful electrophysiology programs, inappropriate implants may occur. A possible result will be that survival of all of these patients will be credited to the ICD, but that fewer will receive shocks than now. That may produce a further but unclear benefit.

Fogoros is correct in saying that the lesson of this controversy is the need for early use of adequate methodology in evaluating any new therapy. For the ICD we come to

such studies late. Careful analysis of large patient populations, based on agreed definitions and statistical techniques, are more likely to provide us with useful information and are very important.

Seymour Furman, MD
Bronx, New York
22 July 1991

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Book: Carrel A, Cutler EC, Gross RE, Blalock A, Craffoord C, Brock RC, Bailey CP, DeBakey ME. The Closing of Holes, Replacing of Valves and Inserting of Pipes, or How Cardiovascular Surgeons Deal with Knives, Knaves and Knots. New York: Yorke University Press, 1984:903.

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ONCE-A-DAY *

ACCUPRIL®

quinapril HCl tablets

escribing, please see full prescribing information. A brief summary follows.

ONS AND USAGE

L is indicated for the treatment of hypertension. It may be used alone or in combination with thiazide diuretics.

ACCUPRIL, consideration should be given to the fact that another angiotensin-converting enzyme (ACE) inhibitor, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease. Available data icient to show that ACCUPRIL does not have a similar risk (see WARNINGS).

NDICATIONS

L is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related is treatment with an ACE inhibitor.

IS

ma: Angioedema of the face, extremities, lips, tongue, glottis, and larynx has been reported in patients treated with ACE and has been seen in 0.1% of patients receiving ACCUPRIL. Angioedema associated with laryngeal edema can be fatal. If stridor or angioedema of the face, tongue, or glottis occurs, treatment with ACCUPRIL should be discontinued imme- e patient treated in accordance with accepted medical care, and carefully observed until the swelling disappears. In where swelling is confined to the face and lips, the condition generally resolves without treatment; antihistamines may n relieving symptoms.

re is involvement of the tongue, glottis, or larynx likely to cause airway obstruction, emergency therapy including, but not subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 mL) should be promptly administered RSE REACTIONS).

on: Symptomatic hypotension was rarely seen in uncomplicated hypertensive patients treated with ACCUPRIL but, as ACE inhibitors, it is a possible consequence of therapy in salt/volume depleted patients, such as those previously treated lics or dietary salt restriction or who are on dialysis (see PRECAUTIONS, DRUG INTERACTIONS, and ADVERSE REAC- controlled studies, syncope was observed in 0.4% of patients (N = 3203); this incidence was similar to that observed for 1%) and enalapril (0.8%).

with concomitant congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may ssive hypotension, which may be associated with oliguria or azotemia and, rarely, with acute renal failure and death. In nts, ACCUPRIL therapy should be started at the recommended dose under close medical supervision. These patients ollowed closely for the first 2 weeks of treatment and whenever the dosage of antihypertensive medication is increased GE AND ADMINISTRATION).

iatic hypotension occurs, the patient should be placed in the supine position and, if necessary, normal saline may be ed intravenously. A transient hypotensive response is not a contraindication to further doses; however, lower doses of or reduced concomitant diuretic therapy should be considered.

ia/Agranulocytosis: Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow rarely in patients with uncomplicated hypertension, but more frequently in patients with renal impairment, especially if ive a collagen vascular disease such as systemic lupus erythematosus or scleroderma. Agranulocytosis did occur during treatment in one patient with a history of neutropenia during previous captopril therapy. Available data from clinical trials IL are insufficient to show that, in patients without prior reactions to other ACE inhibitors, ACCUPRIL does not cause tosis at similar rates. As with other ACE inhibitors, periodic monitoring of white blood cell counts in patients with col- lar disease and/or renal disease should be considered.

atal morbidity and mortality: ACE inhibitors, including ACCUPRIL, can cause fetal and neonatal morbidity and mortal- ministered to pregnant women.

nhibitors have been used during the second and third trimesters of pregnancy, there have been reports of hypotension, , skull hypoplasia, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal gohydramnios has been associated with fetal limb contractures, craniofacial deformities, hypoplastic lung development, rine growth retardation.

and patent ductus arteriosus have been reported, although it is not clear whether these occurrences were due to the r exposure or to the mother's underlying disease. It is not known whether exposure limited to the first trimester can fect fetal outcome.

o becomes pregnant while taking ACE inhibitors, or who takes ACE inhibitors when already pregnant, should be the potential hazard to her fetus. If she continues to receive ACE inhibitors during the second or third trimester of requent ultrasound examinations should be performed to look for oligohydramnios. When oligohydramnios is found, rs should generally be discontinued.

histories of in utero exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. curs, attention should be directed toward support of blood pressure and renal perfusion. Hemodialysis and peritoneal little effect on the elimination of quinapril and quinaprilat.

or teratogenic effects were observed in rats at quinapril doses as high as 300 mg/kg/day (180 and 30 times the maxi- uman dose when based on mg/kg and mg/m^2, respectively), despite maternal toxicity at 150 mg/kg/day. Tested later in during lactation, reduced offspring body weight was seen at ≥25 mg/kg/day, and changes in renal histology (jux- cell hypertrophy, tubular/pelvic dilation, glomerulosclerosis) were observed both in dams and offspring treated with lay. Quinapril was not teratogenic in the rabbit; however, as noted with other ACE inhibitors, maternal toxicity and ty were seen in some rabbits at quinapril doses as low as 0.5 mg/kg/day (one time the recommended human dose) g/day, respectively.

IS

al function: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the nsin-aldosterone system, treatment with ACE inhibitors, including ACCUPRIL, may be associated with oliguria and/or zotemia and rarely acute renal failure and/or death.

dies in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and line have been observed in some patients following ACE inhibitor therapy. These increases were almost always revers- continuation of the ACE inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during eeks of therapy.

nsive patients with no apparent preexisting renal vascular disease have developed increases in blood urea and serum ually minor and transient, especially when ACCUPRIL has been given concomitantly with a diuretic. This is more likely tients with preexisting renal impairment. Dosage reduction and/or discontinuation of any diuretic and/or ACCUPRIL ed.

hypertensive patients should always include assessment of renal function (see DOSAGE AND ADMINISTRATION).

and potassium-sparing diuretics: In clinical trials, hyperkalemia (serum potassium ≥5.8 mmol/L) occurred in 2% of patients receiving ACCUPRIL. In most cases, elevated serum potassium levels were isolated values that ue continued therapy. Less than 0.1% of patients discontinued therapy due to hyperkalemia. Risk factors for the f hyperkalemia include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing ssium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with e PRECAUTIONS, Drug Interactions).

thesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, ACCUPRIL otensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to n, it can be corrected by volume expansion.

r Patients

Angioedema, including laryngeal edema, can occur with treatment with ACE inhibitors, especially following the first should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of s, eyes, lips, tongue, difficulty in swallowing or breathing) and to stop taking the drug until they have consulted with (see WARNINGS).

ypotension: Patients should be cautioned that lightheadedness can occur, especially during the first few days of apy, and that it should be reported to a physician. If actual syncope occurs, patients should be told to not take the have consulted with their physician (see WARNINGS).

uld be cautioned that inadequate fluid intake or excessive perspiration, diarrhea, or vomiting can lead to an exces- d pressure because of reduction in fluid volume, with the same consequences of lightheadedness and possible

ng to undergo any surgery and/or anesthesia should be told to inform their physician that they are taking r.

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Hyperkalemia: Patients should be told not to use potassium supplements or salt substitutes containing potassium without ing their physician (see PRECAUTIONS).

Neutropenia: Patients should be told to report promptly any indication of infection (eg, sore throat, fever) which could be a neutropenia.

NOTE: As with many other drugs, certain advice to patients being treated with ACCUPRIL is warranted. This information is i to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Drug Interactions

Concomitant diuretic therapy: As with other ACE inhibitors, patients on diuretics, especially those on recently instituted di therapy, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ACCUPRIL. Th bility of hypotensive effects with ACCUPRIL may be minimized by either discontinuing the diuretic or cautiously increasing intake prior to initiation of treatment with ACCUPRIL. If it is not possible to discontinue the diuretic, the starting dose of qui should be reduced (see DOSAGE AND ADMINISTRATION).

Agents increasing serum potassium: Quinapril can attenuate potassium loss caused by thiazide diuretics and increase seru potassium when used alone. If concomitant therapy of ACCUPRIL with potassium-sparing diuretics (eg, spironolactone, tria terene, or amiloride), potassium supplements, or potassium-containing salt substitutes is indicated, they should be used wi caution along with appropriate monitoring of serum potassium (see PRECAUTIONS).

Tetracycline and other drugs that interact with magnesium: Simultaneous administration of tetracycline with ACCUPRIL re the absorption of tetracycline by approximately 28% to 37%, possibly due to the high magnesium content in ACCUPRIL tabl This interaction should be considered if coprescribing ACCUPRIL and tetracycline or other drugs that interact with magnesiu

Lithium: Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomit lithium and ACE inhibitor therapy. These drugs should be co-administered with caution, and frequent monitoring of serum lit levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity.

Other agents: Drug interaction studies of ACCUPRIL with other agents showed:

- Multiple dose therapy with propranolol or cimetidine has no effect on the pharmacokinetics of single doses of ACCUPRIL.
- The anticoagulant effect of a single dose of warfarin (measured by prothrombin time) was not significantly changed by quin coadministration twice-daily.
- ACCUPRIL treatment did not affect the pharmacokinetics of digoxin.
- No pharmacokinetic interaction was observed when single doses of ACCUPRIL and hydrochlorothiazide were administered concomitantly.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Quinapril hydrochloride was not carcinogenic in mice or rats when given in doses up to 75 or 100 mg/kg/day (50 to 60 times maximum human daily dose, respectively, on a mg/kg basis and 3.8 to 10 times the maximum human daily dose when based mg/m^2 basis) for 104 weeks. Female rats given the highest dose level had an increased incidence of mesenteric lymph node h ngiomas and skin/subcutaneous lipomas. Neither quinapril nor quinaprilat were mutagenic in the Ames bacterial assay with c without metabolic activation. Quinapril was also negative in the following genetic toxicology studies: in vitro mammalian cell mutation, sister chromatid exchange in cultured mammalian cells, micronucleus test with mice, in vitro chromosome aberrat with V79 cultured lung cells, and in an in vivo cytogenetic study with rat bone marrow. There were no adverse effects on fertil reproduction in rats at doses up to 100 mg/kg/day (60 and 10 times the maximum daily human dose when based on mg/kg a mg/m^2, respectively).

Pregnancy

Pregnancy Category D: See WARNINGS, Fetal/Neonatal morbidity and mortality.

Nursing Mothers

It is not known if quinapril or its metabolites are secreted in human milk. Quinapril is secreted to a limited extent, however, in of lactating rats (5% or less of the plasma drug concentration was found in rat milk). Because many drugs are secreted in hum milk, caution should be exercised when ACCUPRIL is given to a nursing mother.

Geriatric Use

Elderly patients exhibited increased area under the plasma concentration time curve (AUC) and peak levels for quinaprilat com to values observed in younger patients; this appeared to relate to decreased renal function rather than to age itself. In controlle uncontrolled studies of ACCUPRIL where 918 (21%) patients were 65 years and older, no overall differences in effectiveness o safety were observed between older and younger patients. However, greater sensitivity of some older individual patients cannc ruled out.

Pediatric Use

The safety and effectiveness of ACCUPRIL in children have not been established.

ADVERSE REACTIONS

ACCUPRIL has been evaluated for safety in 4960 subjects and patients. Of these, 3203 patients, including 655 elderly patients, participated in controlled clinical trials. ACCUPRIL has been evaluated for long-term safety in more than 1400 patients treated f 1 year or more.

Adverse experiences were usually mild and transient.

Discontinuation of therapy because of adverse events was required in 4.7% of patients treated with ACCUPRIL in placebo-conti hypertension trials.

Adverse experiences probably or possibly related to therapy or of unknown relationship to therapy occurring in 1% or more of th 1563 patients in placebo-controlled hypertension trials who were treated with ACCUPRIL are shown below.

Adverse Events in Placebo-Controlled Trials

	ACCUPRIL (N = 1563) Incidence (Discontinuance)	Placebo (N = 579) Incidence (Discontinuance)
Headache	5.6 (0.7)	10.9 (0.7)
Dizziness	3.9 (0.8)	2.6 (0.2)
Fatigue	2.6 (0.3)	1.0
Coughing	2.0 (0.5)	0.0
Nausea/Vomiting	1.4 (0.3)	1.9 (0.2)
Abdominal Pain	1.0 (0.2)	0.7

Clinical adverse experiences probably or possibly related, or of uncertain relationship to therapy, occurring in 0.5% to 1.0% (exc as noted) of the patients treated with ACCUPRIL (with or without concomitant diuretic) in controlled or uncontrolled trials (N = 4397) and less frequent, clinically significant events seen in clinical trials or post-marketing experience (the rarer events ar italics) include (listed by body system):

General: back pain, malaise

Cardiovascular: palpitation, vasodilation, tachycardia, *heart failure, hyperkalemia, myocardial infarction, cerebrovascular accide hypertensive crisis, angina pectoris, orthostatic hypotension, cardiac rhythm disturbances*

Gastrointestinal: dry mouth or throat, constipation, *gastrointestinal hemorrhage, pancreatitis, abnormal liver function tests*

Nervous/Psychiatric: somnolence, vertigo, syncope, *nervousness, depression*

Integumentary: increased sweating, pruritus, *exfoliative dermatitis, photosensitivity reaction*

Urogenital: *acute renal failure*

Other: amblyopia, pharyngitis, sinusitis, bronchitis, *agranulocytosis, thrombocytopenia*

Angioedema: angioedema has been reported in patients receiving ACCUPRIL (0.1%). Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis, and/or larynx occurs, treatment with ACCUPRIL should be discontinued and appropriate therapy instituted immediately. (See WARNINGS.)

Clinical Laboratory Test Findings

Hematology: (See WARNINGS)

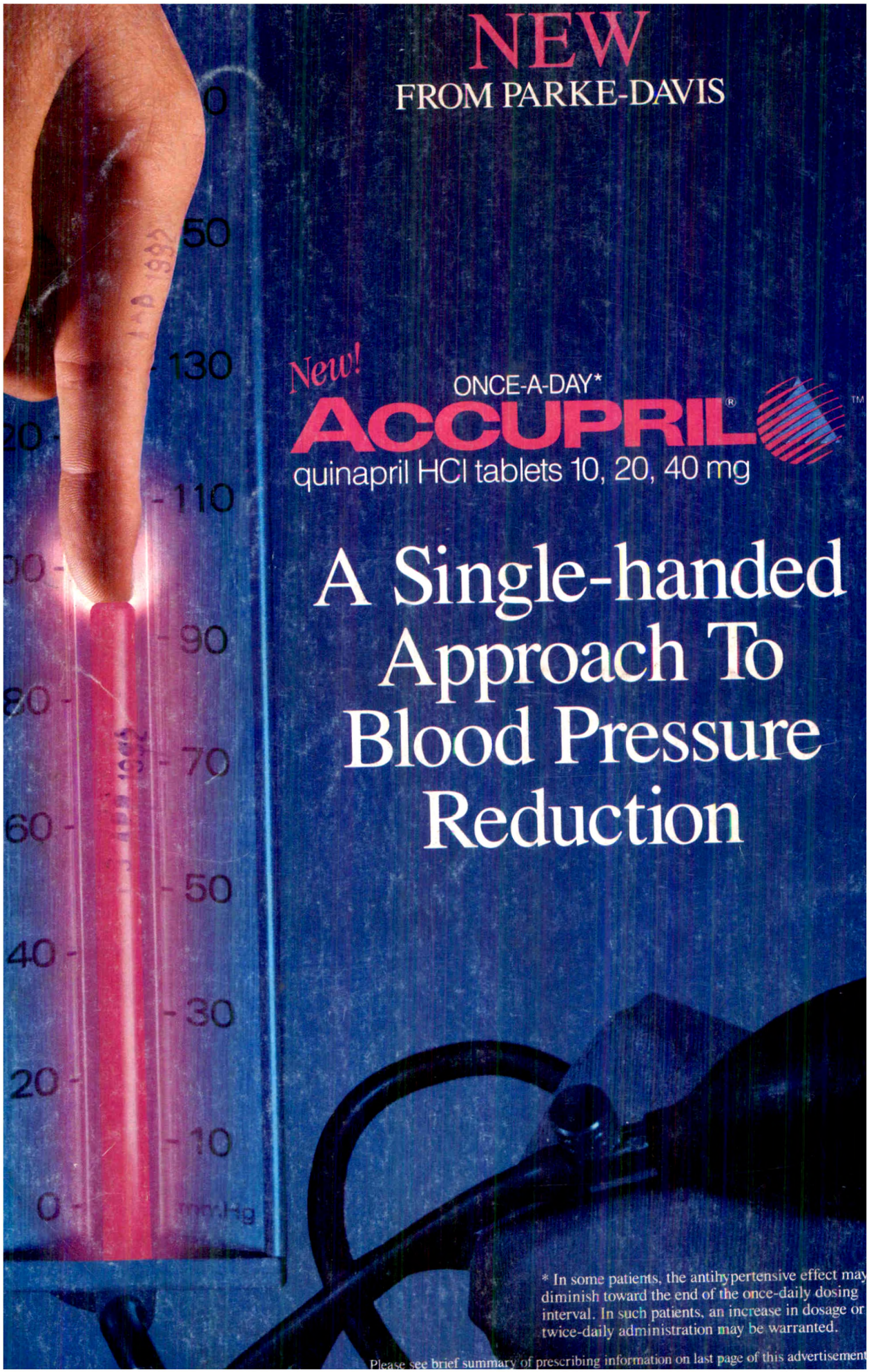
Hyperkalemia: (See PRECAUTIONS)

Creatinine and blood urea nitrogen: Increases (>1.25 times the upper limit of normal) in serum creatinine and blood urea nitrog were observed in 2% and 2%, respectively, of patients treated with ACCUPRIL alone. Increases are more likely to occur in patients receiving concomitant diuretic therapy than in those on ACCUPRIL alone. These increases often remit on continued therapy.

* In some patients, the antihypertensive effect may diminish toward the end of th once-daily dosing interval. In such patients, an increase in dosage or twice-daily administration may be warranted.

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